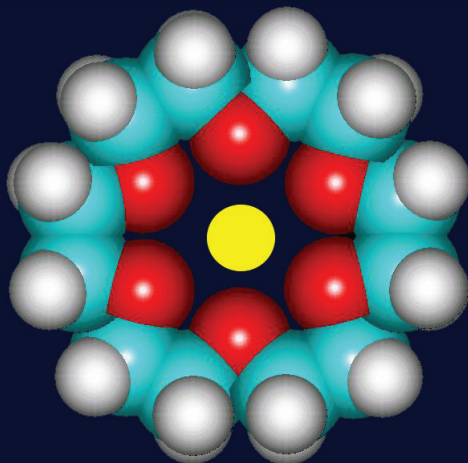# From concept to

molecular receptor

Edited by

Volodymyr I. Rybachenko

From concept to molecular receptor

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Contents

Preference

The book "From concept to molecular receptor" is next monograph with range of supramolecular chemistry. Supramolecular chemistry is often defined as being "chemistry beyond the molecule". While traditional chemistry focuses on the covalent bond, supramolecular chemistry examines the weaker and reversible noncovalent interactions between molecules. These forces include hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, pi-pi interactions and electrostatic effects. According to J-M. Lehn, who invented the term, a supermolecule is an organized, complex entity that is reated from the association of two or more chemical species held together by intermolecular forces. Supermolecule structures are the result of not only additive but also cooperative interactions, including hydrogen bonding, hydrophobic interactions and coordination, and their properties are different than the sum of the properties of each individual component.

Molecular receptors are this specialized molecules which on receiving environmental stimuli information produces an informative. The scientific term that have been demonstrated by supramolecular chemistry include molecular self-assembly, folding, molecular recognition, host-guest chemistry, mechanically-interlocked molecular architectures, and dynamic covalent chemistry. The world of molecular receptors is this at present one of the most important areas of modern chemistry.

Prof. V. I. Rybachenko

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Chapter 1

"Click chemistry" – facile way of synthesizing macromolecules

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The term „click chemistry" was coined by B. Sharpless at al [1] to describe the way of constructing diversified molecules by joining different "building blocks" *via* reliable, efficient and universal chemical reaction. The reaction should ideally be devoid of side products (enabling minimal purification procedure – avoiding chromatography) and leave no unreacted substrates. Among different classes of organic reactions (examples being epoxide opening by a nucleophile, carbonyl addition, Diels-Alder cyclization) the 1,3-dipolar addition of an azide to terminal (sometimes even inner) alkyne stems as the one almost totally fulfilling the requirements. It is high-yield reaction which needs no harsh conditions, has little substituent effect (except large steric crowding) and yields stable, neutral product [2].

Both elements of the "snap joint" i.e. azide and alkyne are easily introduced into building blocks *via* numerous procedures, enabling convenient access to preformed "parts" of the desired molecule. These "parts" can then be assembled in exactly required order.

Since click reaction occurs in aqueous solutions, in conditions which can be adapted close to physiological, it is easily applied to biomolecules – peptides, proteins, enzymes, nucleic acids, and can proceed even inside living cells [3,4,5,6].

Mechanism of the reaction

Huisgen 1,3-dipolar addition [7] of organic azide to the carbon-carbon triple bond occurs without catalyst only after long time and at elevated temperature. It is also non-regiospecific, giving the mixture of 1,4- and 1,5- disubstituted 1,2,3-triazoles. Only with highly electron-deficient terminal alkynes preference toward formation of 1,4-isomers is observed.

1,4-isomer   1,5-isomer
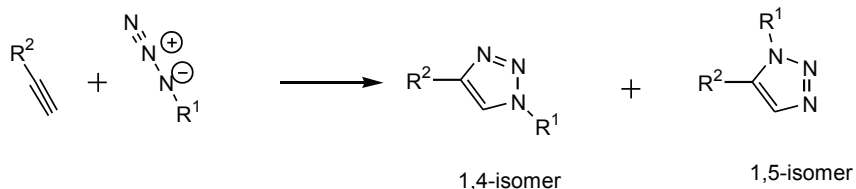
*Scheme 1. Huisgen 1,3- dipolar cycloaddition*

This changes dramatically upon Cu^I ion catalysis. The reaction is greatly accelerated (10^7 times) and exclusively 1,4-disubstitited 1,2,3-triazole is formed. The rate of the reaction allows performing it without heating and it can be accomplished within minutes. Large number of functional groups can be present in reacting molecules without any harm to the outcome of the synthesis. It is also worth to notice that substrates – azide and alkyne are also inert to most organic compounds or biomolecules. [8,9]

The Cu^I catalyst can be introduced in the form of a cuprous salt or can be formed *in situ* by reducing Cu^{II} ion by appropriate reducing agent (ascorbate is the most popular one, although tris(2-carboxyethyl)-phosphane hydrochloride was also used with success [10])

Another possibility is reducing of Cu^{II} with metallic copper (comproportionation) or oxidation of the metal, which sometimes can be beneficial [11]. Detailed mechanism of the reaction is not yet fully clarified, but enough evidence is gathered to propose its possible pathway (Scheme 2).

Limitations of the scope of the reaction are really small. Except obvious obstacles of solubility, susceptibility of other substituents to the conditions or availability of reactants, only strong electron-withdrawing substituents close to azide group can slow the reaction and lower the

yield. For example fluorine-substituted azides react sluggishly [2] and sulfonyl-substituted azides give rise to N-sulfonylamides instead of triazoles [12]. In contrast to this, electron-deficient alkynes react readily. Steric strain plays role only in extreme cases.
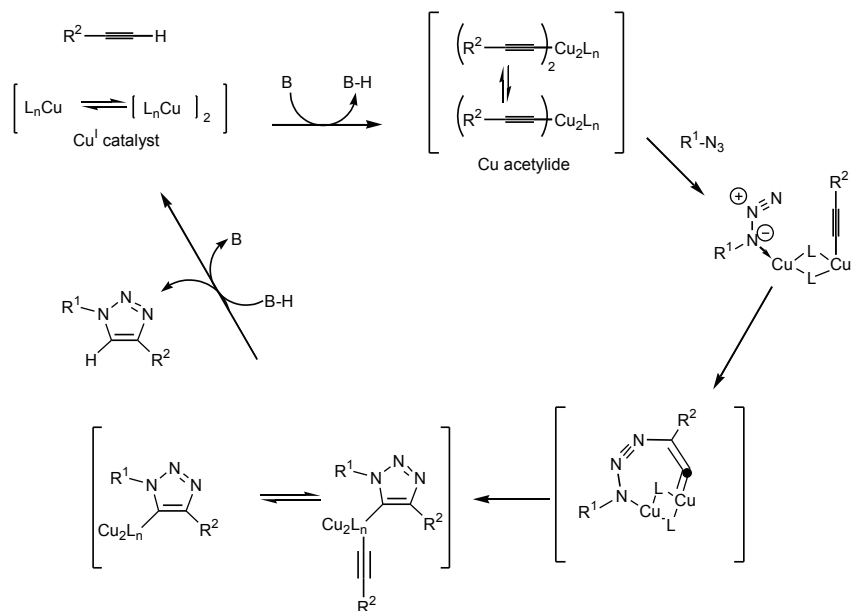
Scheme 2. Accepted mechansm of Cu^I-catalysed reaction of azide and alkyne

Applications of click chemistry

Ease of coupling of different molecules with the 1,2,3-triazole linker was utilized in many synthetic and analytical applications, concerning both scientific research and commercial products.

These include attaching numerous probes to a solid support, creation of drug libraries, fingerprinting of enzyme inhibitors, labeling or coupling of receptor-attached substrates (enzyme studies), assembling of dendrimer polymers, carbohydrate or protein immobilization, construction of nanostructures and many other.

Materials science

Dendrimer synthesis often requires tedious purification and isolation

steps. These problems are greatly solved by applying stepwise click reaction for the synthesis of the dendrimer. The process can be ordered by first constructing I[st] generation of polymer, which bears inactive substituent, easily convertible into azide or alkyne (for example halogen atom). As click reaction runs in stoichiometric proportion of reagents and proceeds to almost completion, the product requires little or no purification. Over-polymerization does not occur because of the absence of further reacting azide or alkyne. Azide group is introduced into I[st] generation product by efficient substitution reaction with sodium azide and IInd generation can then be synthesized. The process can be repeated giving rise to polymer of very well defined structure and high purity. this mode of action fails only after IVth generation, probably because of diffusion problems [13].

Possibility of breaking the polymerization process into isolated steps enables constructing of star shaped "mictoarm" structures, i.e. stars with arms of different structure [14]. Reacting tripropargylamine with excess of azide-derivatised polymer (for example polystyrene) gave intermediate product A, which then could be reacted with azide derivatives of different polymers, leading to mictoarm stars. Repeating this process with different combinations of linear polymers lead to the array of mictoarm structures [14]

X,Y = polystyrene, poly(methylacrylate),
poly(t-butylacrylate)

Mictoarm star polymer
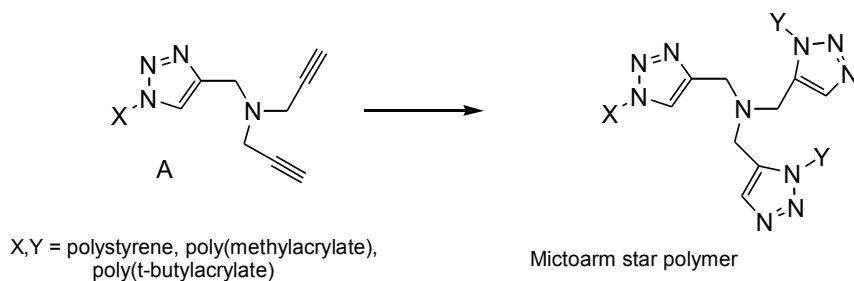
Figure 1. Synhesis of mictoarm polymers

Introducing uncommon units into polymer (for example carbohydrate moieties) often poses great problem because of their reactive groups and difficulty in regulating the amounts of introduced unit. Glycosides with azido or alkyne substituents are readily available. Two such glycosides (glucose and mannose derivatives) were attached to polystyrene chain

equipped with alkyne appendages. Ratio of the attached carbohydrate residues directly reflected stoichiometry [15]. Such "neoglucopolymers" are of great interest because of their promising medical applications.

Solid supported synthesis became over the years one of crucial tools for the assembly of complicated macromolecules, especially peptides and oligonucleotides [16]. Possible is also reverse application – attaching of different reagents to a solid support which simplifies their use and removal from the reaction mixture or allows applying in flow-through reaction systems. In each case reliable way for attaching different molecules to the support is necessary. Click reaction is perfectly suited for the purpose. It was applied for preparation of triazolyl methyl acrylate resin [17], which served in constructing library of tertiary amines,

Agarose is commonly used chromatography matrix in separation or isolation of biomolecules, It is often modified with ligand residues specific for desired molecule, which preferentially associate with it and separate it from the mixture - the technique being called affinity chromatography. Agarose can be derivatized with azide and then "custom" decorated with specific ligand (which is prepared with alkyne group attached). It allows to prepare as much of affinity material as is needed for the given chromatography separation, without wasting precious ligand [18].

Click reaction is much more controllable than radical polymerization, routinely used for cross-linking of linear polymers. Since degree and distribution of cross-link bonds affects the properties of cross-linked polymer, more precise way of introducing cross-links gives better way of controlling properties. It is especially important when the polymer is to be used in medicine (for example hydrogels [19]).

Thermally unstable organogel

Stabilised organogel
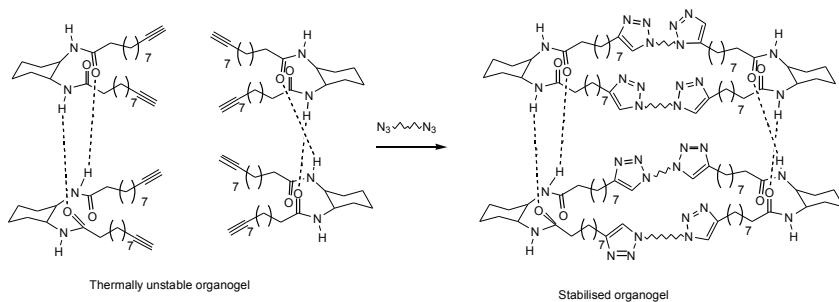
Scheme 3. Stabilization of organogels

Using variety of cross-linking bis-azides gave the possibility to tune the properties of the gel to specific needs.

Monolayer carbon nanotubes attracted great interest and found applications which include molecular electronics, sensors, field emission devices or composite materials. These applications often depend on the possibility of proper manipulation of the material during preparation of the composite or nanostructure. Low solubility of carbon nanotubes can be major obstacle in these operations. Nanotube grafted with acetylene residues could be coated with polystyrene chains *via* the click-chemistry process. Without losing their unique properties such prepared nanotubes gained solubility in number of solvents [20]

Functionalized carbon nano-tube
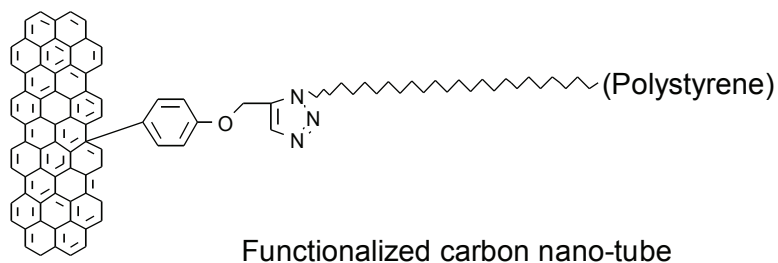
Triazoles exhibit strong affinity to metal surfaces. It was shown, that mixture of alkyne and azide introduced between two metallic surfaces (made of copper-containing alloys) lead to strong adhesion of these surfaces. Force of attachment outperformed commercial glues. Trace cuprous ions extracted from metal provide enough catalytic effect for such glue to become effective [21].

As could be expected, the reaction of such potential was not neglected also in the field of supramolecular chemistry. One example are calixarenes possessing lipophilic cavities which were coupled to hydrophilic chains by the reaction shown. The product . gained water solubility which greatly expanded its possible field of application [22].
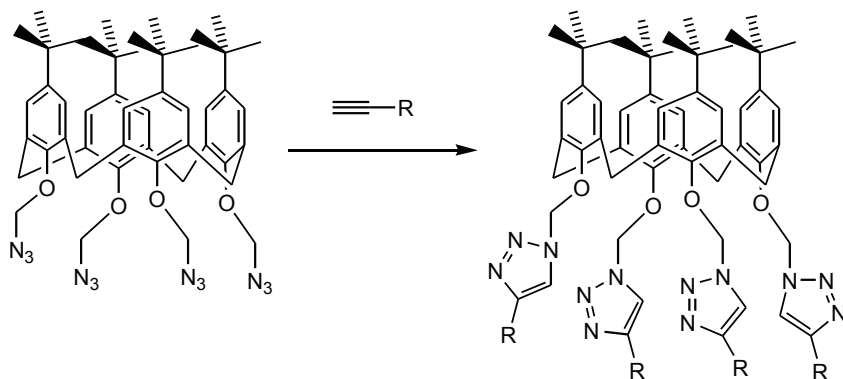
Solubilised calixarene   (R = sulfonyl, tertiary amine, glukonamide)

Figure 2. Calixarenes with hydrophilic chains

Analytical applications

Construction of sensors specific for given molecules or ions creates the possibility to detect and estimate target compounds in crude mixtures or biological samples without the need of prior isolation or separation. Astruc et al [23] constructed dendrimer molecule containing in its structure up to 81 ferrocene residues. Synthesis proceeded easily, with the alkynyl ferrocene as the source of the sensing group. As was shown by cyclic voltametry studies, the dendrimer selectively reacted for oxo anions (ATP^{-2} or $H_2PO_4^-$) without interference from other anions. The same sensor was useful also in recognition of transition metal cations.

Kumar and Pandey [24] noticed that triazole ring can take part in hydrogen bond and dipole-dipole interactions. By modifying bile acid-based azide with different substituents and changing the surrounding of the triazole residue they were able to construct receptor which showed selectivity to halogen anions ($F^->Cl^-> Br^-> I^-$) or to phosphate exclusively. Triazole moiety participated in anion complexation through its H5 hydrogen atom.
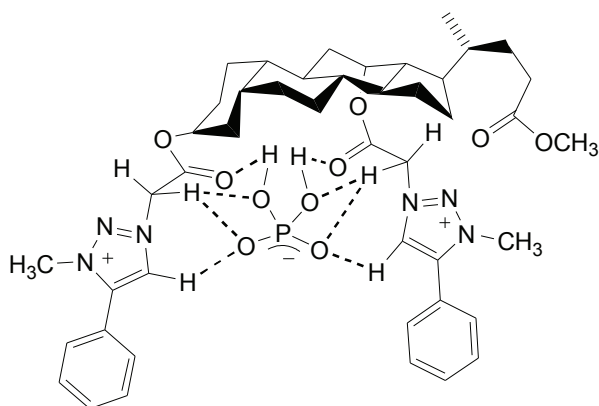
Figure 3. Bile acid-derived phosphate-selective ligand

Bioconjugation

Bioconjugation covers wide range of modifications concerning biomolecular framework. Most often it means attachment of synthetic labels to the framework. Labels cover several classes of compounds, such as chelates, ligands, radioisotopes, fluorophores, affinity or immunoassay tags. Bioconjugation can also mean coupling together two or more biomolecules into a larger one (for example fusing carbohydrates with proteins or producing covalently linked peptide associates).

Click chemistry exploits the fact that azide functionality is not present in any of the known natural compound, therefore no accidental undesired side-products are possible.

DNA molecule, constructed via the automated synthesis with alkyne substituted uridine monomer (A or B) was post-synthetically functionalized with different probes by reaction with appropriate azide derivatives [25].
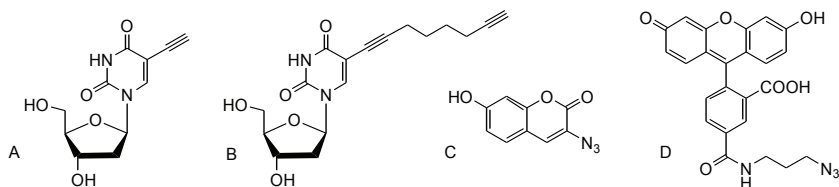

Figure 4. Alkyne-dervatized deoxyuridine units and azide-derivatized fluorescent dyes used in DNA labeling

Among the labels attached, coumarine derivative C is especially interesting, as it fluoresces only after triazole formation. During this synthesis catalytic Cu^I ion was stabilized with specific ligand tris(benzyl triazolylmethyl)amine [26]. The stabilization was necessary, due to the ability of cuprous ion to degrade DNA in aqueous solution.

Short peptides can be conveniently ligated into larger protein-like (peptoid) structures utilizing click-chemistry. Three peptidic azides were attached in sequence onto cyclic peptide which served as a scaffold for the whole structure
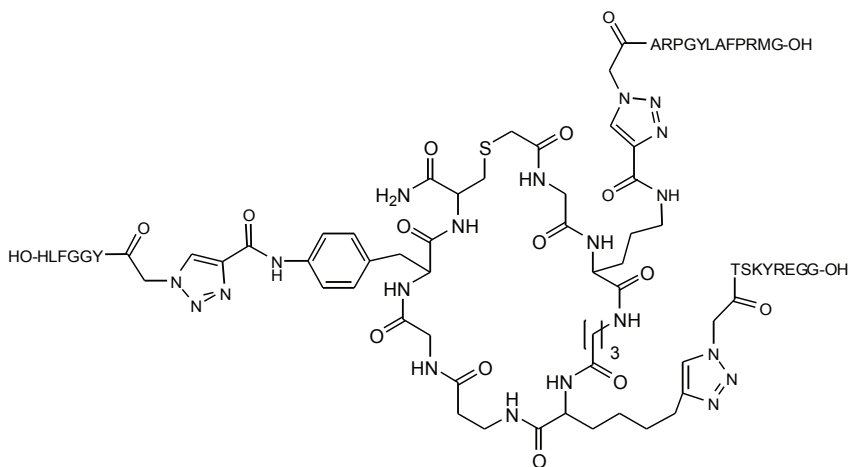

Figure 5. Cyclic peptide decorated with three oligopeptide chains

Immobilization of biomolecules onto solid surface without losing their activity has gained great importance in constructing microarrays, biosensor chips or microbeads [27]. Limitations arise from the fact that attachment to solid surfaces is often accompanied with denaturation, wrong orientation or unwanted reactions close to active site of the biomolecule. These obstacles can be omitted if the biomolecule is attached to the solid surface via neutral linker of proper length. Glass surface can be easy coated with polyoxyethylene chains bearing alkyne group at the end, which serves an "anchoring point" for azide-substituted biomolecules [28].

In this interesting example two reactions deserving the name "click" were utilized. The linker was equipped with two different reactive

groups at both ends: cyclopentadiene and alkyne. First the linker itself was attached to the glass surface via the Diels-Alder reaction between cyclopentadiene group and maleimide-modified glass. In the next step alkyne from the other end captured azide group present in biotin derivative. This sequence led to biotin secured to the glass, but with linker separating it from the surface.
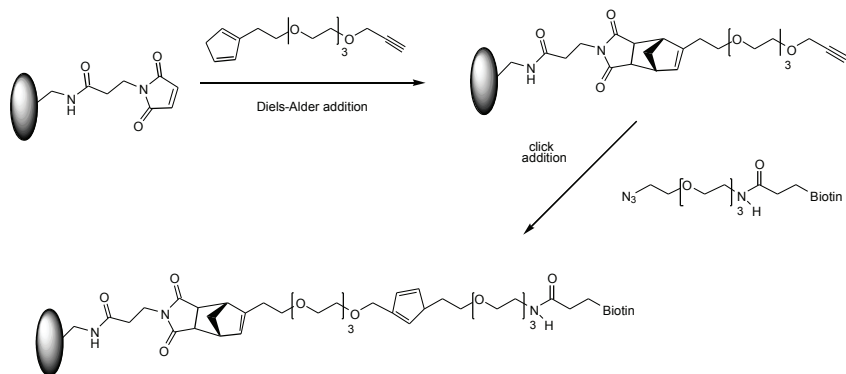

Figure 6. Biotin-derivatized glass

Obviously, there is number of methods which can be used for the surface derivatization, but alkyne-azide chemistry offers mild conditions, acceptable for fragile functional groups, thus avoiding the need for protection-deprotection steps. For example earlier mentioned agarose [18] could be modified with aldehyde-based affinity substituent directly, while other procedures required three-step synthesis.

Finn at al. [29] studied conjugation of different molecules to the surface of cowpea mosaic virus. Free amino groups present at the surface of the virus protein coat (residues of lysine) or thiols (residues of cysteine) were instrumental as the points of attachment of azido and alkynyl substituents. These in turn were employed to bind fluorescent dyes via the click reaction. The reaction conditions applied initially were harmful for the virus, causing its decomposition. Again it turned out that stabilization of Cu^{I} ion with complexing ligand alleviated its aggressiveness towards the virus protein.
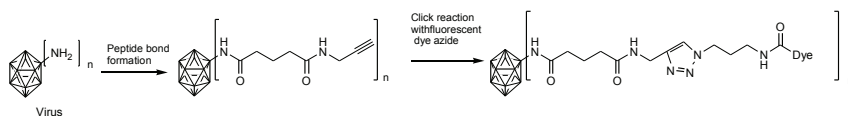
*Figure 7. Labeling of cowpea mosaic virus with fluorescent dye*

Detailed studies led to modified complexing agent (batophenantroline derivative), which required much smaller excess of the labeling substrate. This procedure was successful in preparing virus particles conjugated with carbohydrates, peptides, polyoxyethylene polymers or even proteins (transferrin) [29].

Enzyme activity in relation to its structure remains one of major streams of research in molecular biology. Many different methods are applied, one of the most promising is activity based protein profiling. It consists of reacting the studied protein with the probe molecule provided with two key elements: reactive group, interacting with the active site of the enzyme (or even covalently binding to it) and second group which has the properties allowing for convenient detection. Such a system is able to fish out the protein which has the studied affinity or activity from a complicated mixture. The major difficulty is that the reporter molecule is usually quite large and can not penetrate through the cell wall. It requires homogenization of studied cells or even organellae prior to experiment (*in vitro* technique). Destroying of the cell structure can considerably affect the enzyme activity and influence the results.

By using the probe in the form of two subunits, smaller and easier to introduce into the cell, it was possible to conduct the experiment *in vivo*. Subunits were equipped with alkyne and azide appendages and after the affinity part was absorbed by the enzyme inside the cell, second unit (reporter) was applied and reacted with enzyme-associated probe. This procedure was effective in studying acetylcholinesterases [30] carboxyesterase-1 (CE-1) [31] glutathione S-transferase, enoyl CoA hydratase, aldehydedehydrogenase [32] or fatty acid amide hydrolase [33]. Also highly selective probe for serine/threonine kinase was developed [34]. The applications of click chemistry in catalomics were recently reviewed [35].

When employing click chemistry in living or biological systems, one has to be always aware of possible unwanted activity of necessary

copper ions. Bertozzi et al proposed promising approach which utilizes high energy alkyne. The "spring-loaded" cyclooctyne has enough inner energy arising from steric strain, that no catalyst assistance is needed to overcome activation threshold of the click reaction. Azide-functionalized Chinese hamster cells were incubated with the biotynylated cyclooctyne and labeling of the cells was observed. Cells without azide functionality did not react with the probe., [36,37]
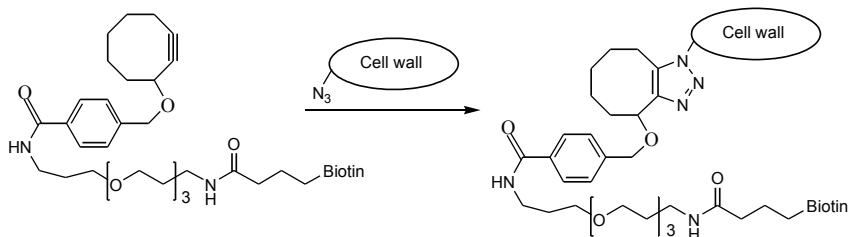
Scheme 4. "Spring-loaded" cyclooctyne reacting without the need of catalyst

Medicinal chemistry

Initial step of every drug development is screening of large array of chemical compounds – possible candidates. This "library" ideally should contain all possible diversifications of the matter structure i.e. matter core with substituents of all required sizes, functionalities, positions of attachment etc.

For example when inhibitor of enzyme r-1,3-fucosyl transferase was developed, known facts about transition state of catalyzed reaction indicated presence of sugar donor, sugar acceptor, divalent metal and nucleotide. It was also known that hydrophobic pocket is located near the active site and that GDP-fucose is involved.

By reacting 85 azide fragments of different structure with alkyne derivatized GDP library of possible inhibitors was created, out of which three were active. Scale-up and further tests showed one of them to be potent inhibitor and after further adjustments first known inhibitor of this enzyme working at nanomolar concentration was synthesized [38].

It was also proved that 1,4-substituted triazole group has pharmacophoric properties by itself [39].

Planar triazole based structure had the virtue of stabilizing G-quadruplexes, known to be crucial in regulating the function of

telomerase. This enzyme is believed to be responsible for the "immortality" of cancer cells, and stable G-quadruplexes inhibited its action. The effect was noticeable even in the presence of large excess of duplex DNA.
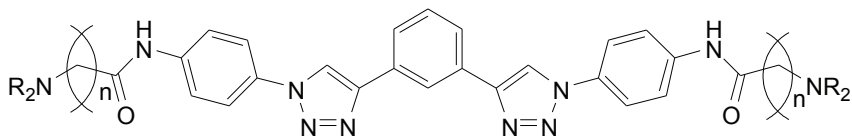

Figure 8. G-quadruplex-stabilizing polyaromatic

Novel method in the discovery of new drugs is the target-guided synthesis. It comprises of mixing together of fragment molecules with complementary reacting groups (azide and alkyne). The molecules should exhibit weak affinity to target biological structure (enzyme, regulatory protein etc). If the mixture is applied to the target, these fragments associate with target molecule , and if they are arranged in close contact their complementary "click" groups are in convenient position for the coupling reaction. The reaction produces larger molecule of considerably greater affinity to he target. This way target does not choose from the library of inhibitor molecules, but from the library of substrates and promotes the synthesis of proper inhibitor structure. Recent review of Sharpless and Manetsch [40] lists numerous examples of succesful syntheses *via* this approach. It utilizes intrinsic properties of the Huisgen 1,3-cycloaddition: the reaction is thermodynamically very favorable, but is extremely slow due to high energy of activation. Association of the molecules onto target active site lowers this energy and allows for the coupling of attached fragments. In fact target substitutes plays the role of the Cu^I ion, but does it much more selectively, choosing from the array of possible fragments only the ones which form effective inhibitor. It is worth to mention that reaction without promotion by the target is extremely slow in the conditions applied (extrapolated 80% completion after 40 years [40]).

Acetylcholinesterase [41] when subjected to this experiment promoted synthesis of 34 pairs (out of 98 possible) of known weak inhibitors (tacrine and phenantridinium derivatives) arranged in different stereochemical relations. Also numerous other enzymes were successfully tested in this approach, among them HIV-1 protease [42,43].

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Chapter 2

Molecular scavengers-the variety of applications

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Scavengers are generally defined as substances added to a mixture in order to remove or inactivate impurities. They are used in efficient solution phase combinatorial chemistry, in which chemical synthesis is carried out in solution phase and then the reaction mixture is purified by a solid support (Figure 1), [1].
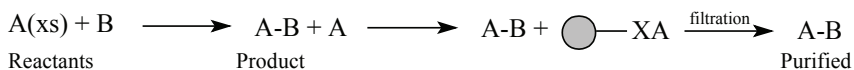
$$A(xs) + B \longrightarrow A\text{-}B + A \longrightarrow A\text{-}B + \bigcirc\!-XA \xrightarrow{\text{filtration}} A\text{-}B$$

Reactants   Product   Purified

Figure 1. Schematic reaction involving molecular scavenger

However, the above-mentioned definition concerns scavenger reagents applied in organic synthesis. The scavenging property of systems discussed can be also applied in chromatography, extraction of cations, catalytic or ion-exchange reactions [2].

Typical molecular scavenger consists of solid surface (inorganic support including magnetic nanoparticles or polymeric support) and immobilized functional groups that are attached to the support directly or via spacer (Figure 2).

The available scavengers are divided into two different classes – ionic (acidic or basic reagents) and covalent (electrophilic or nucleophilic reagents), (Figure 3).
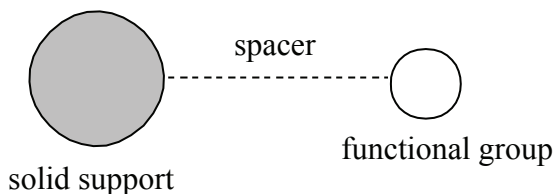
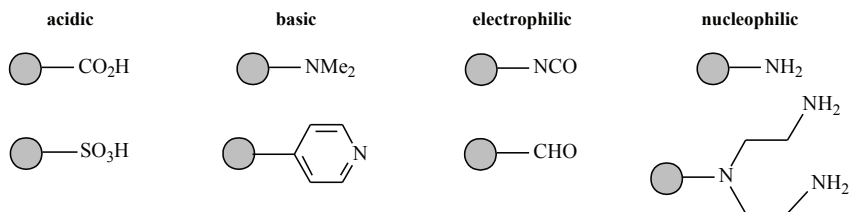*Figure 2. Schematic representation of molecular scavenger*

Figure 3. Examples of different classes of molecular scavengers

This short review concerns exemplary applications of molecular scavengers divided dependently on solid support type.

1. Molecular scavengers with inorganic non-magnetic supports

Inorganic solid supports consist of different oxides like Al_2O_3, SiO_2, TiO_2, MgO, NiO, ZnO, CeO_2 or ZrO_2 and lamellar like mica, graphite, MoS_2. Unlike polymeric supports, they are characterized by good selectivity, no swelling, rapid sorption of metal ions and good mechanical stability. Such supports are wildly modified in laser dispersing process to obtain metal-ceramic composite that are used *inter alia* as catalysts [3-5]. The process is based on local melting of the ceramic by a CO_2 laser beam and it changes thermophysical properties of starting material, leading to the reinforcement of the mechanical strength and an enhancement of the thermal conductivity. Ceramic substrate materials are generally modified by a deposition of following metals Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag, Re, Os, Ir and Pt. Such metal/oxide interface finds many applications like novel structural materials, metal/oxide seals in devices and medical implant construction, metal/oxide contacts in microelectronics and photovoltaic devices, coatings for corrosive passivation, gas-sensors and oxide-supported transition metal catalysts [6].

The surface modification happens either physically or chemically. It assumes not only metal immobilization but different functional groups as well. The most popular inorganic support is silica, which is able to immobilize the variety of organofunctional groups. The scavenging property of functionalized silica gel is used in the extractive concentration of metal ions, which allows partial elimination of toxic heavy elements from wastewater. Some examples of immobilization of organic reagents/chelating groups on silica surface are presented in Table 1.

The popularity of silica gel as solid support comes from many aspects. First of all, it was the first commercially available substrate of such a type. It allows the immobilization of great variety of silylating agents that facilitate the incorporation of different functional groups into inorganic framework. Moreover, silica gel is thermally stable and it is characterized by high resistance to organic solvents and no swelling.

Table 1. The exemplary organofunctionalized silica

Chelating group	Application
Thiosemicarbazide	Separation and selective extraction of Pd(II) [7];
2,4-Dichlorophenoxyacetic acid	Separation and preconcentration of Cu^{2+}, Ni^{2+}, Zn^{2+} and Cd^{2+} [8];
Ethylenediamine derivatives	Sorption of Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} [9];
Pyrazole derivatives	Selective adsorption of Cu^{2+} [10];
Resacetophenone	Preconcentration of Cd^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Fe^{3+} and Ni^{2+} [11];
Purpurogallin	Selective extraction and preconcentration of Fe^{3+} [12];
Phosphonic acid	Sorption of lanthanide ions [13];
Tetraphenylporphyrin	Complexation of Sn(IV), In(III), Zn(II) [14];
3-(Mercapto)propyl derivative	Selective preconcentration of Hg^{2+} [15];
Dithioacetal derivatives	Solid phase extractor for Hg(II) [16].

2. Molecular scavengers with inorganic magnetic supports

Magnetic iron oxides Fe_3O_4 or γ- Fe_3O_4 represent specific solid surface. It can be magnetized with an external magnetic field if only having suitable particle size [17]. Moreover, such magnetic oxides are stable and harmless to the living bodies. Those specific properties decide that iron oxide is predominantly used, despite other 'more magnetic materials' available

(based on cobalt, nickel, gadolinium or others). Magnetic nanoparticles offer attractive applications in the field of biotechnology – as nucleic acid separation, cell separation, drug delivery system, magnetic resonance imaging and hyperthermia. Some of the application attracts particular attention as those systems are used for early detection of cancer, diabetes and atherosclerosis. However, it requires surface modification in order to facilitate binding to a biological entity (Figure 4). Such material must also be targetable delivery with particle localization in a specific area. It means that if it binds drugs, the attached material is trapped in a target site after magnetic field applying [18].
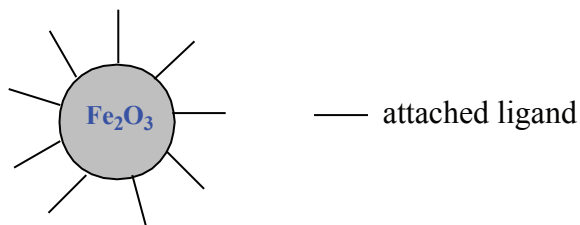

Figure 4. Schematic representation of modified iron oxide surface

The exemplary synthesis of modified iron oxide nanoparticles presents Figure 5 [19]. Firstly, supermagnetic nanoparticles are obtained, while following magnetic nanoparticle 1 (MNP 1) comes from the coprecipitation of iron(II) and (III) chlorides under basic conditions. Further transformation is carried out in sol-gel process with 3-aminopropyltrimethoxysilane to give amino terminal group of MNP 2. Iron oxide undergoes the aggregation. Then linker, suberic acid bis-N-hydroxysuccinimide ester (DSS), is added to combine aminosilane and anti-serum amyloid P component (anti-SAP) antibody, and to give anti-SAP antibody-conjugated MNPs. Such ethylene glycol-protected nanoparticles could be applied as multiplexed immunoassay in human plasma.

The application of new functionalized iron oxide nanoparticles in magnetic resonance imaging comes from limited spatial resolution of commercially available contrast agents, which disables individual cells

or molecules prevention. Such agents are trapped in a macromolecular matrix like dextran. However, the replacement of mentioned matrix by PEG-gallol and PEG-dopamine, stabilizing agents, provides increased particle stability and smaller diameters compared to above-mentioned. Those PEGylated nanoparticles can be modified by using PEG-chains that bear functional groups [20].
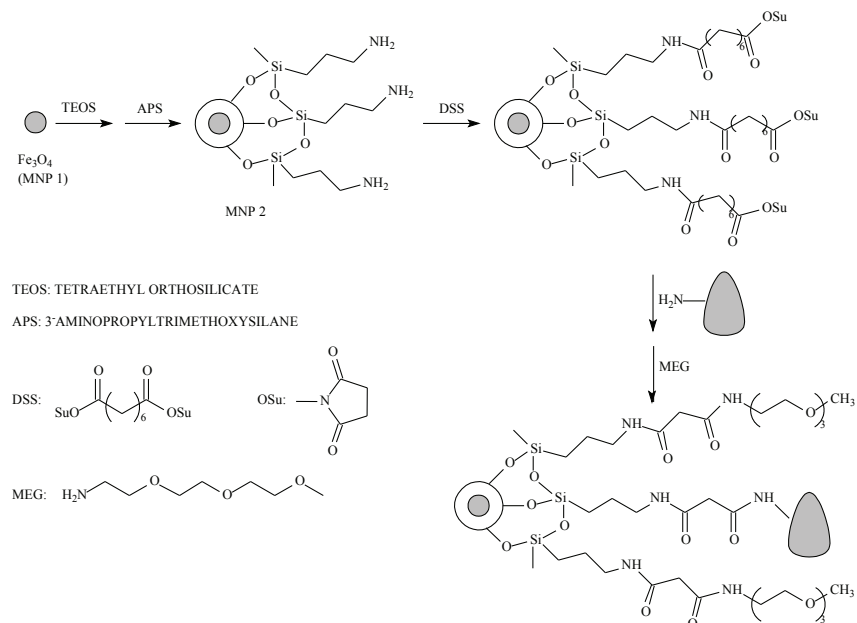

Figure 5. Synthesis of MEG-protected antibody-conjugated MNPs

Despite common utilization of the magnetic separation technology in biomedical application, it is rarely used in the recovery of valuables and catalysts. The modification of magnetic particles with thiol groups gives effective scavenger for palladium ion from solutions (Figure 6), [21]. Firstly iron oxide nanoparticles are coated with oleic acid and then it is reacted with 3-mercaptopropionic acid to give final product with thiol terminal groups. Such effective palladium scavenger presents another option beside extraction and filtration procedures.
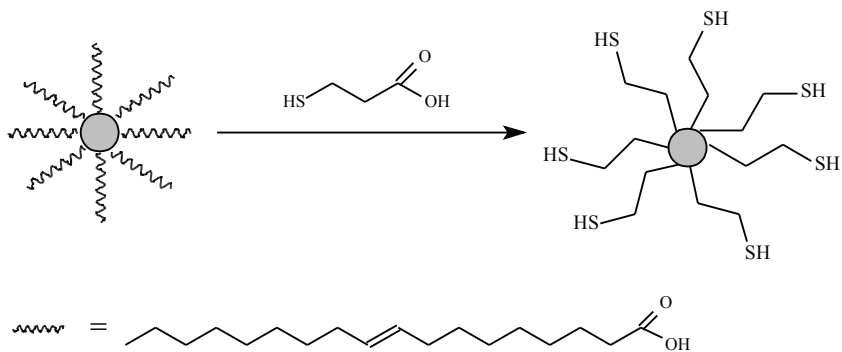
Figure 6. Synthesis of thiol-modified magnetic nanoparticles

3. Molecular scavengers with polymeric supports

Ionic and covalent polymeric scavengers are used in organic synthesis. The beginning of polymer supported reagents in synthetic application started from the synthesis of amides and sulfonamides using different electophilic reagents. Complementary polymeric scavengers were used to remove the excess reagents and the resulting HCl (Figure 7), [22].
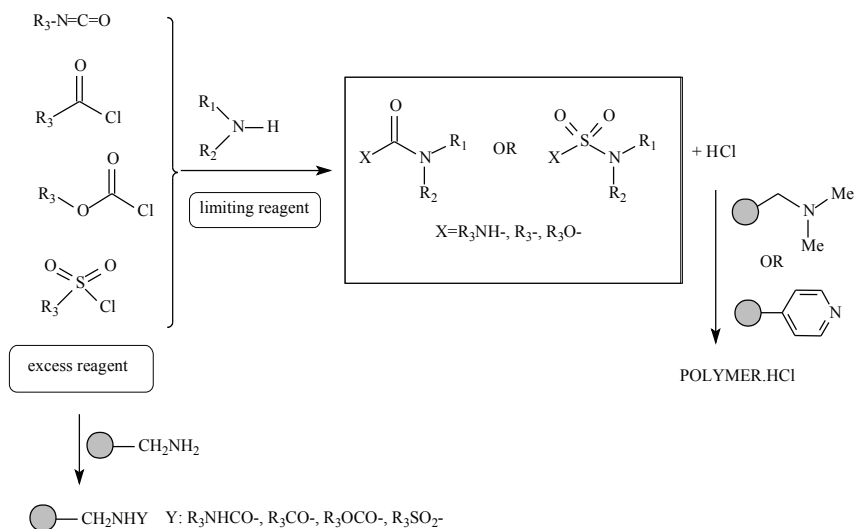

Figure 7. Polymer supported resins as purification agents

Another three polymer supported reagents (**A**, **B**, **C**) were applied individually or in combinations in a solution phase synthesis of ureas, thioureas, sulfonamides, amides and pyrazoles (Figure 8), [23].
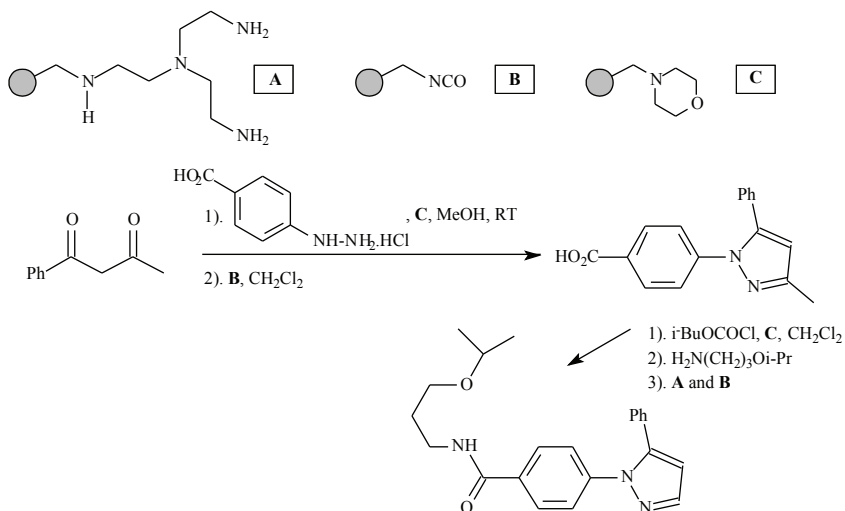

Figure 8. Pyrazole synthesis with three different polymer scavengers

The covalent isocyanate scavenger **B** was used in both reactions steps, while **A** and **C** ones (polymeric triamine and morpholine respectively) were applied as polymeric supported bases to remove easily reaction impurities. Moreover the application of all scavengers in the second multireaction step ensures efficiency.

Highly basic polymeric base PTBD (1,5,7-triazabicyclo[4.4.0] dec-5-ene) demonstrates ion exchange property in *O*- and *N*-alkylation experiments (Figure 9), [24]. The reaction of substituted phenols with scavenger PTBD gives ionic PTBD-H^{+} with more nucleophilic phenolate. Addition of electrophile R-X provides aryl ethers ROAr. The applied scavenger removes H-X produced and *ipso facto* the extraction procedure is eliminated.

Different 2,4-pyrrolidinediones were obtained following the procedure presented at Figure 10 [25]. The polymeric base, ammonium ion exchange resin, promotes cyclisation in the initial reaction step and retains cyclised product in the consecutive one. In acidic environment,

the final product is easily eluated from the scavenger and it represents excellent purity and yield.
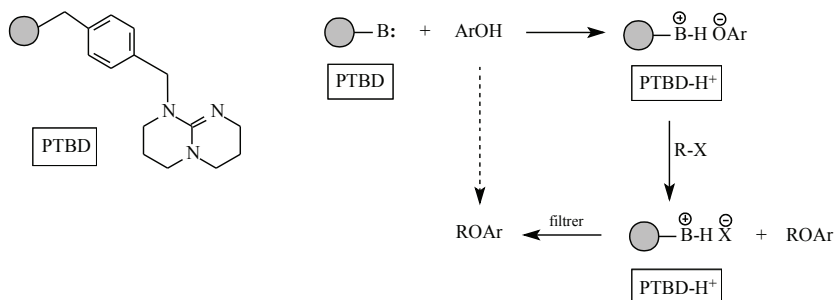

Figure 9. Synthesis of aryl esters with ionic scavenger PTBD
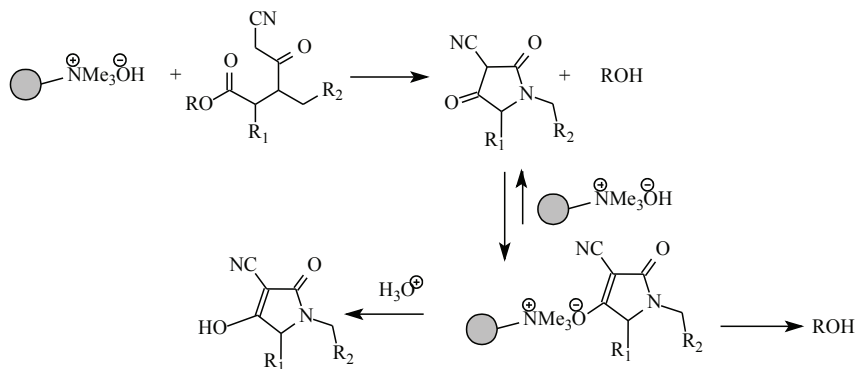
Figure 10. Synthesis of 2,4-pyrrolidinediones with different R_1 and R_2 substituents

The number of scavengers available for boronic acids is limited. On the other hand such acids are wildly used as intermediates and in the biological recognition. A polymer scavenger presented at Figure 11 [26] is applied in aryl boronic acid synthesis. (N,N'-diethanolaminomethyl) polystyrene purifies crude reaction product by capturing the boronic acid. Then purification process is much easier because it only requires rinsing of the resin bound.

Figure 11. Synthesis of dienylboronic acid with purifying scavenger

The examples presented show that polymeric scavengers improve significantly the efficiency of solution phase chemistry and facilitate the purification process of organic synthesis products.
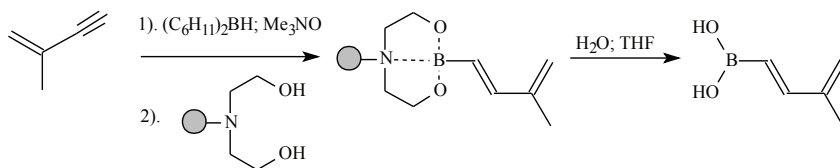
All solid supports discussed contribute to different aspects of human life. The advantages of their application in medicine, environment protection and purification, valuable substance recovery or organic synthesis are invaluable.

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Chapter 3

Solid support in design and synthesis of supramolecular units

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Introduction

The pioneering work of Letsinger [1] and Merrifield [2] on solid-phase organic synthesis has become a widely used tool for rapidly constructing large compound libraries. The concept of solid phase synthesis broadly, has its roots in Mcrrifield's seminal work on peptide synthesis. In the following decade, considerable research focused on extending the methodology to the synthesis not only small organic molecules, but also huge development supramolecular systems. Nowadays laboratories worldwide contributed to pioneering work in the use of polymers as supports, reagents and catalysts. In contrast to the application of solid phase synthesis to peptides and oligonucleotides, significant use of the methodology by the synthetic organic community only materialized recently.

The wide adoption of combinatorial and parallel strategies for compound synthesis in the drug discovery process provided the stimulus that has propelled a dramatic increase in the use of solid phase organic synthesis (SPOS). Concomitant with the resurgence of SPOS has been the development of new polymeric supports aimed at expanding tire scope of the technique.

This article will focus on adduce of advances and disadvantages of different resins for solid phase synthesis and use them to design and synthesis of supramolecular systems. It also discuss polymer synthesis properties and synthetic examples with using of polymer support.

Solid phase synthesis - historical perspective

In solid-phase synthesis, the substrate undergoing transformation is covalently attached to the support material and the reagents and/or coupling partners are present in solution. Following a transformation, the material is purified by a sequence of washing steps to elute solution-labile impurities, before a cleavage step is performed to liberate the functionalized product from the support, thereby enabling its isolation in a pure form.

Application of solid-phase reagents, catalysts, and scavenging techniques presents an attractive alternative to linear, substrate-bound synthesis. This approach embraces many of the advantages of conventional solution-phase chemistry such as real-time reaction monitoring, convergency, and rapid optimization, but also enables purification by the simple expedient of filtration to remove the spent reagents. These techniques also readily accommodate multistep processes, parallel methods, batch-splitting, and reaction scale-up [3].

The first serious application of supported species was in the formation of ocadec-9-enoic acid butyl ester using a sulfonic acid resin in 1946 [3]. The 1950s saw further advances in the form of acidic and basic ion exchange techniques, which are still used as scavengers and buffers in water treatment plants today.

The 1990s, however, heralded a dramatic change in the use of supported reagents in synthesis. Underlying this was the recognition by the pharmaceutical industry as to better make greater numbers of compounds in response to high-throughput screening capability. This led to the concepts of combinatorial chemistry, which was widely adopted by the supramolecular chemistry in design new recognition compounds.

Polymer supports – general considerations

The primary function of a solid support is to provide an inert carrier for a synthetic substrate. Ideally support serve this purpose without significantly affecting the course of the chemical reaction. It is well known that functional groups on polymers have reactivity that approximates that of their small-molecule analogs however, the 'pendant' macromolecule can affect the course of a reaction as a result of steric, electrostatic and diffusion effects.

In the case of cross-linked polymer beads, commonly referred to

as resins, reactions can be influenced by the accessibility of reagents to reaction sites and the microenvironment associated with the polymer phase within the bead.

The most commonly resins used in solid phase synthesis are derived from lightly cross-linked polystyrene, polyethylene glycol (PEG)-grafted polystyrene and macroporous polystyrene. Polystyrene resins are more widely used as they have greater chemical stability. Tile overwhelming preference for beads as a support format has largely limited resin candidates to those based on styrene and acrylates, because of the requirements for suspension polymerization. An important alternative to beads are macroscopic objects, for example pins, based on grafted polyolefins, which have found widespread use in combinatorial parallel synthesis [4].

However, while polystyrene is the most commonly used support, it is certainly not the only material used in solid phase synthesis. The encapsulation of catalysts inside polymeric matrices is one class of reagent involving polymers in an innovative way. Alternative supports such as controlled pore glass, monoliths [5], cellulose [6], zeolites [7] and silicas have also been used [8].

An important aspect of solid phase synthesis is the diffusion of reagents to the reactive sites on bound molecules. For lightly cross-linked polystyrene and PEG graft resins it is generally required that the beads swell in the reaction solvent, establishing a phase that is approximately 10-20% polymer and 80-90% solvent. The mobility of polymer bound molecules and reactants within the swollen gel is directly related to the level of swelling. Macroporous polystyrenes are highly cross-linked porous resins and allow reagent diffusion through a pore network within the beads, rather than through spaces between beads in a swollen polymer gel [4].

The mainly advantages of solid phase synthesis relative to solution phase synthesis are easiness of purification, selective product cleavage and restriction of reaction sites. The most compelling advantage of solid phase synthesis is the ease of purification, in which reactants and by-products not incorporated in the resin-bound molecule are readily removed by repetitive solvent washing. The simplicity of product purification and isolation allows on automation of multistep synthesis employing instrumentation based on fluid delivery and filtration .Since

bound impurities are not readily separable, solid phase synthesis demands the use of robust, high yield reactions to achieve final products of high purity after cleavage from the support.

Polymer supports – constitution of resins.

In methodology using solid phase synthesis have been successfully adopted to perform many organic synthesis, acknowledged that kind of choice of the resin and reaction condition is very important to achieve planned theretofore product.

Reagents using in SPOS are with the functionalized solid matrix. Commonly, this support is divinyl benzene (DVB) cross-linked form of polystyrene. These polystyrene resins can be either micro- or macroporous, depending on the degree of cross-linking. The majority advantages of polystyrene supports are not only cheap but are also easy to handle, achieve high loadings, and, importantly are relatively chemically inert.

Uncrosslinked, or linear, polystyrene is dissolved in hydrophobic solvents and precipitate in protic solvents. This interesting property has been exploited by Chen in a synthesis of prostaglandin $F_{2\alpha}$ [9]. Polystyrene resins swell adequately in most common organic solvents, however, this is dependent upon their cross-linking. Microreticular resins are defined by a low level of cross-linking (1–2% DVB) and swell more easily than their macroreticular counterparts (>30% DVB).

Even though the cross-linked polystyrene resins are insoluble in organic solvents, they are solvated and swollen by aprotic solvents such as toluene, dimethylformamide (DMF), and dichloromethane (DCM). One gram of 1% DVB cross-linked resin will swell 4 to 6 times of its original volume in DCM. In contrast, one gram of 2% DVB cross-linked resin swells only 2 to 4 times of its original volume in DCM. Consequently, resin that swells more will have a higher diffusion rate of reagents into the core of the matrix, resulting in shorter reaction times and more complete chemical conversions [10].

Macroporous polystyrene resins are styrene-divinyl benzene co-polymers that is why they have an internal pore structure. They are usually prepared by carrying out polymerization in the presence of a non reactive diluents that phase separates during the polymerization and defines the pore structure (Figure 1).

Reagents are often transported through the pore structure rather than

through spaces within a polymer gel. When high cross-linking levels are employed, the functionality is largely confined to the pore surface and is accessible to reagents in solvents that are not good swelling solvents for lightly cross-linked polystyrene. The polymeric microglobules showed in Figure 1 are heterogeneous, consisting of highly cross-linked nodules with lower cross-linking at the surface, which is a result of the higher reactivity of divinylbenzene relative to styrene in the polymerization [4].
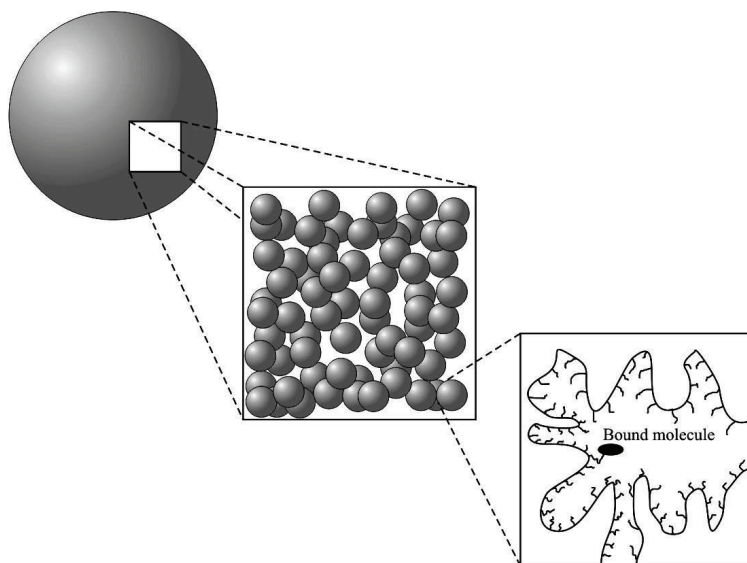

Figure 1. Structure of a macroporous resin.a) ArgoPore TM bead b) Microglobules (c) The internal pore structure [4].

Polystyrene beads are commercially available in sizes ranging from less than a micron to 750 microns in diameter. Reaction kinetics are generally faster using smaller beads due to the higher surface area to volume ratio. Beads in the range of 75 to 150 microns in diameter offer a good balance of reaction kinetics versus reliability. Bead size is commonly reported in Tyler Mesh size which is inversely proportional to the nominal diameter. Two commonly used resin sizes are 100-200 mesh and 200-400 mesh (75-150 microns and 35-75 microns respectively) [10].

Resins for Solid Phase Synthesis

Currently many chemical companies carries polystyrenes resins in a variety kinds and sizes depending on destination. This article will focus on adduce of advances and disadvantages of different resins for solid phase synthesis and use them to design and synthesis of supramolecular systems. It also briefly discuss polymer synthesis properties and synthetic examples with using of polymer support.

Brominated polystyrene is a core resin useful for preparing a variety of derivatized polystyrene resins. This resin is very useful to perform the Suzuki reaction [11]. Another important use is in preparing lithiated polystyrene, used to prepare many other functionalized polystyrenes, such as polystyrene-supported phosphines, silanes, boronic acid, thiol [12].

Shi [13] used brominated polystyrene resin to synthesize combinatorial libraries of unsymmetrically substituted tetra-meso-phenyl porphyrins. Attachment of porphyrin derivatives (onto brominated resin gave a convenient scaffold for the synthesis of photoactive porphyrin libraries with three points for generating diversity. This method allow to use a Suzuki coupling on solid phase (Scheme 1).

The most fundamental substituted polystyrene resin is chloromethylated polystyrene, commonly called Merrifield resin [2], standard support for the synthesis of peptide acids by Boc strategy from many years. In 1984 Robert Bruce Merrifield received the Nobel Prize for his work of the peptide synthesis on solid phase. Substrates are attached to Merrifield resin by nucleophilic displacement of chlorine. Attachment of C-terminal residue is achieved by heating the resin in DMF with the appropriate amino acids cesium salt in the presence of KI, although Me_4N salts, sodium salts in THF with Bu_4NF catalysis and zinc salts in EtOH have been also used [14]. The resulting resin-substrate bond generally is acid stable and requires strong acid conditions for cleavage, what can be considered as disadvantage. Cleavage is normally effected by treatment of resin with HF or TFMSA, or by hydrogenolysis [15].

Kyung-Ho Park and co-workers [16] used Merrifield resin for synthesis of novel hydantoin-containing heterocycles (Scheme 2). Hydantoin is important medicinal and agrochemical moiety, modified extensively for various biological applications.
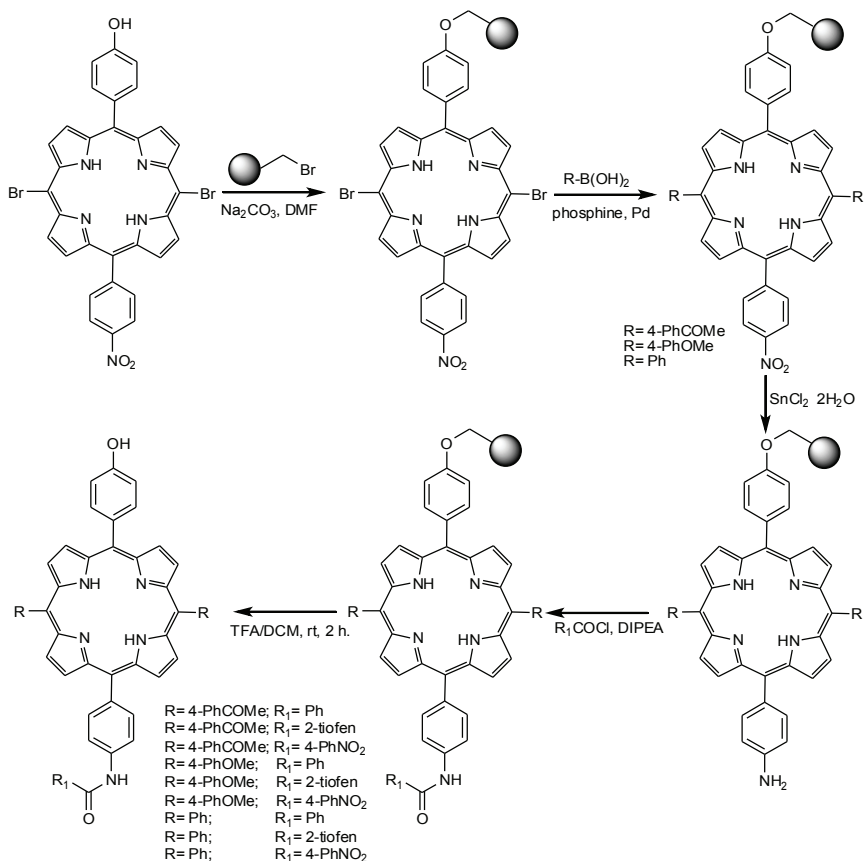
*Scheme 1. Synthesis of library of unsymmetrically substituted porphyrins.*

Since the Merrifield resin-substrate bond is stable to most reaction conditions in solid phase synthesis, a wide array of synthesis resins, scavenger resins, and polymer-supported reagents have been prepared by attaching appropriate linkers to Merrifield resin as it was widely used supramolecular chemistry [17-18].

One of many examples of modifications Merrifield resin is a synthesis of the triazines showed by Bräse [19], who synthesized a new linker for aliphatic amines on solid support. The Merrifield resin in the first stage was treated with *m*-hydroxyaniline in the presence of sodium hydride and then *t*-BuONO in the presence of trifluoroborane–etherate in THF at

−10 ℃. Resulting the diazonium resin salt after washed was treated with various amines in dichlorometane (DCM) at −10 ℃ to room temperature receiving appropriate amines (Scheme 3). The products was obtained with excellent overall yield and what is most important, with high purity after cut-off by treatment with 10% trifluoroacetic acid from resin
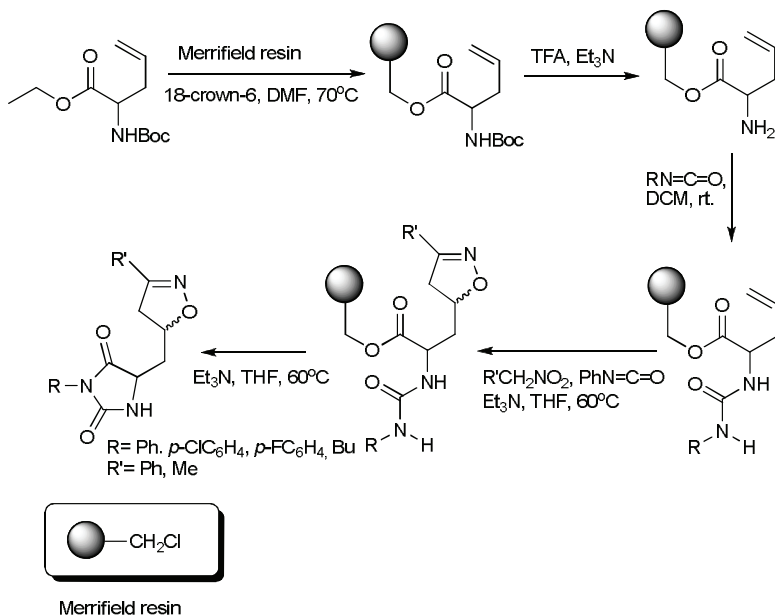
Scheme 2. Synthesis of hydantoin derivatives on Merrifield resin.
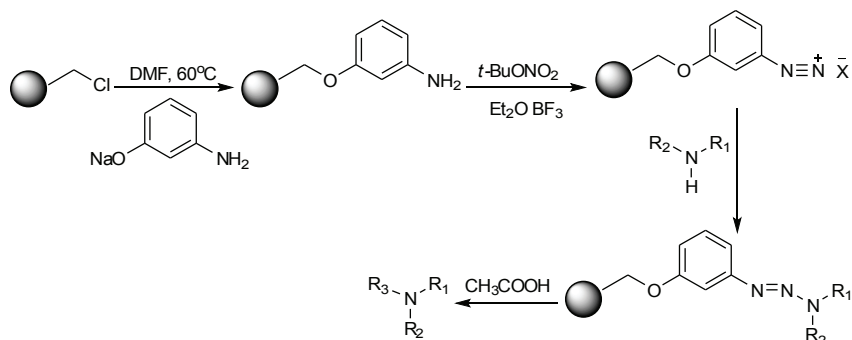
Scheme 3. Usage of Merrifield resin for the synthesis of derivatives amines.

Merrifield resin, as well as many other substituted resins, is generated by one of two methods: by direct incorporation of the substrate onto the polymer core through an electrophilic aromatic substitution reaction or copolymerization of the substituted monomer with styrene.

Merrifield resin, typically is a mixture of isomers 70% of *para*-and 30 % of *meta*-chloromethyl substitutents. Copolymerization allows the use of purified monomers, enabling the preparation of resins with up to 98% *para* substituent. Such resins, exhibit greater swelling factors that result in faster, higher yield reactions. Additionally, the substitution of the resin can be precisely controlled by adjusting the relative proportions of styrene and substituted monomer. That is why many manufactures produce resin using both techniques allowing custom preparation of nearly any combination of size, substitution and crosslinking [10] .

Merrifield resins are commonly used for synthesis of molecular scavengers. Scavengers are supported compounds that selectively sequester by-products from a reaction and render them insoluble such that they can be readily removed by filtration (Figure 2).Their use can be highly effective at improving the purity profile of complex reaction streams without resorting to liquid–liquid extractions or column chromatography. Scavengers can exploit both ionic and covalent interactions, and bind either organic or inorganic impurities. In the simplest of cases, electrophilic or nucleophilic by-products are removed by reciprocally functionalized supports [3].
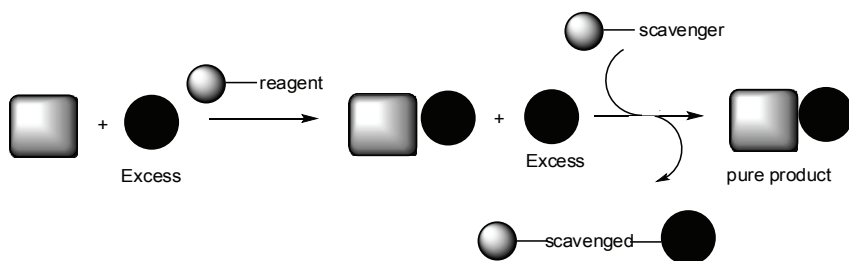

Figure 2. Removal of excess components using supported scavengers.

Using of the scavengers is very effective and economical that is why scavengers find widespread applied in many reaction. Their use have influence to improve the purity of the products and often the time of

reaction is significantly shortened.

Coppola [20] shows the synthesis of new scavenger resin for amines, which completely removes primary and secondary aliphatic amines from reactions used in excess, what found use in many chemical reactions. Using of this resin due to receive the highly pure reaction product.

Those scavenger was received by attachment to the Merrifield resin isatoic anhydride in the presence of sodium hydride (Scheme 4a). Isatonic anhydride is an internally protected and activated form of 2-aminobenzoic acid (Scheme 4b). The C-4 carbonyl of the heterocyclic ring is highly susceptible to attack by the variety of nucleophiles to give open form of the ring, along with carbon dioxide as the only by-product.
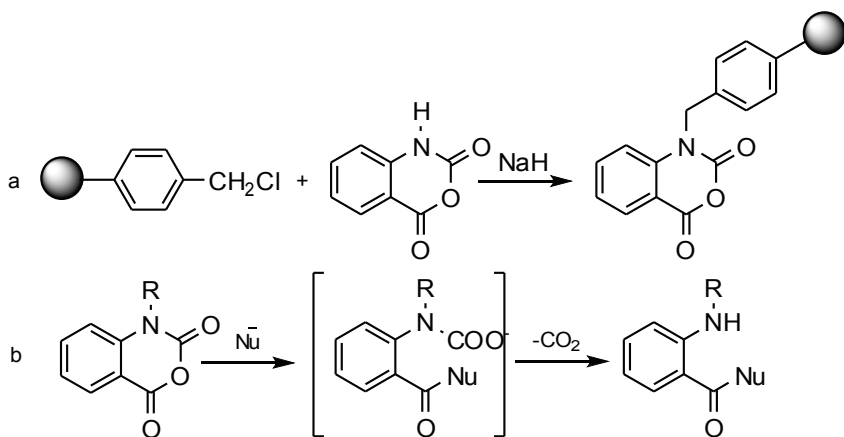
Scheme 4. Scavenger resin for amines a) the method of synthesis, (b) the mechanism of reaction.

Shortell [21] and his co-workers used the Merrifield's resin and the Agropore resin, a highly crosslinked polystyrene to reaction of cyclization of oligo(*m*-phenylene ethynylene) in pseudo high dilution condition on polymer support. As a result of synthesis proved that, the lightly crosslinked Merrifield's resin was inadequate to provide desire macrocyclic product (Scheme 5). The obtained pentamer in the reaction of polymere-supported cyclization instead of cyclic expected octamer create linear heptamer.
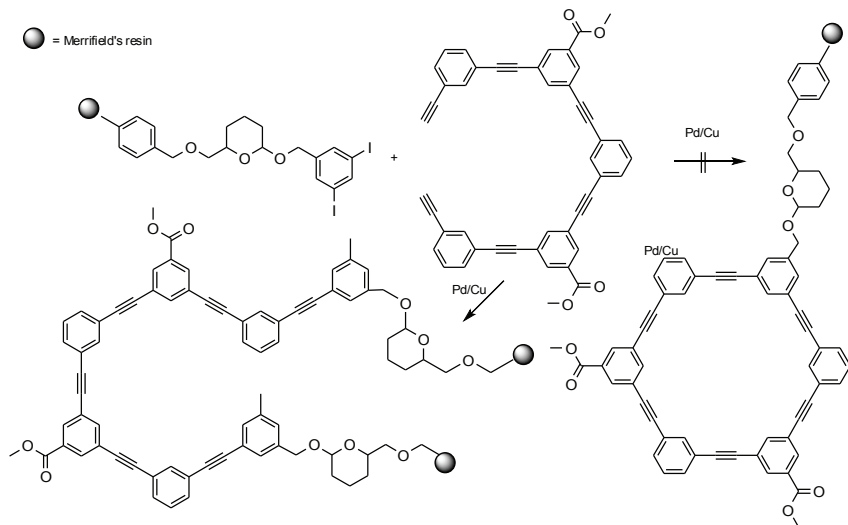
Scheme 5. Synthesis of oligomers with using of Merrifield's resin.

However, if the same synthesis was carried out on Agropore resin, a more highly cross-linked resin in the same conditions, the expected product was obtained with satisfactory yield (Scheme 6).
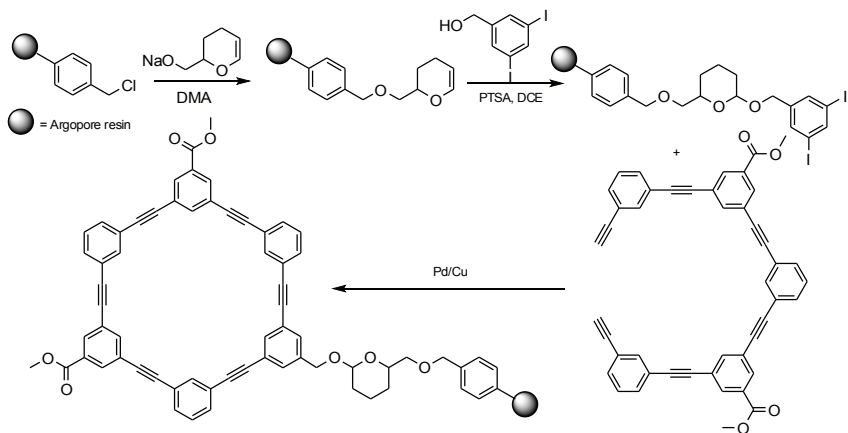
Scheme 6. Synthesis of oligomers with using of Agropore resin.

It is turned out, that attempts to isolate pure cyclic oligo(*m*-phenylene ethynylene) failed. Surprising the relationship after being cut from resin creates a structure of catenane threated inside the polymer network (Scheme 7).
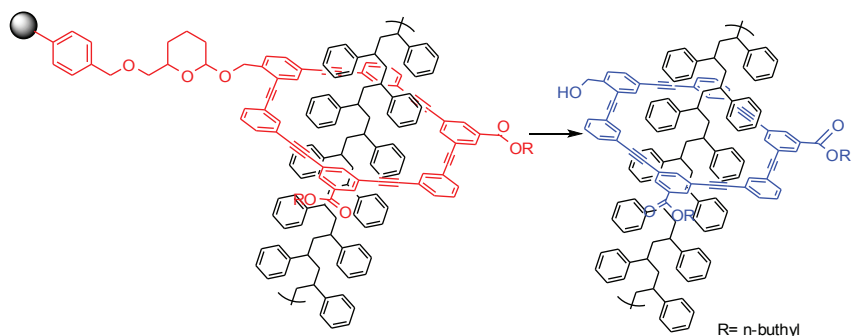

Scheme 7. Effect of the cleavage reaction on the Agropore resin-bound cyclic hexamer.

The Merrifield's resin found widespread use in the production of polymeric ion-exchange resins. These derivatives usually include units capable to specifically and selectively binding ions of metal, what found application in environmental analysis.

Merrifield's resin is usually used to synthesize various chelating polymeric resin. Vinod [22], synthesized by covalently linking calix[4] arene-o-vanillinthiosemicarbazone through its 'lower rim' to Merrifield resin (Scheme 8). Calixarenes, are considered as the third generation of supramolecules, which have a molecular framework with 'upper rim' and 'lower rim' that can be separately and selectively modified with different functionalities to achieve metal complexing properties and the desired solubility characteristics. Obtained resin was efficiently employed to separate and preconcentrate toxic metal ions such as Cu(II), Cd(II) and Pb(II) in in naturally water samples.

Kim [23-24], was modified Merrifield's resin by crown ethers to exploited it for the chromatographic purposes. Using 4'-aminobenzo-18-crown-6 (Scheme 9), and 4'-aminobenzo-15-crown-5 (Scheme

10), bonded on Merrifield peptide resin, he examined lithium isotopes separation by cation exchange chromatography.
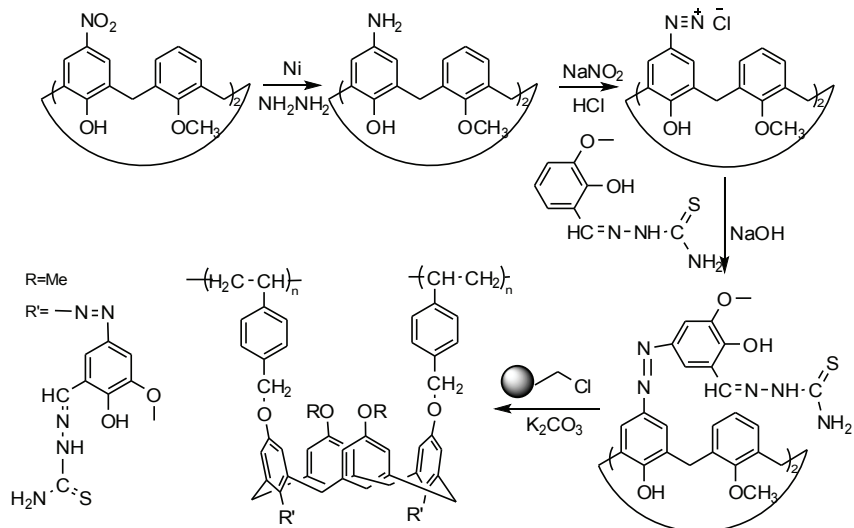
Scheme 8. Synthesis of modified resins by Calixarenes molecule.
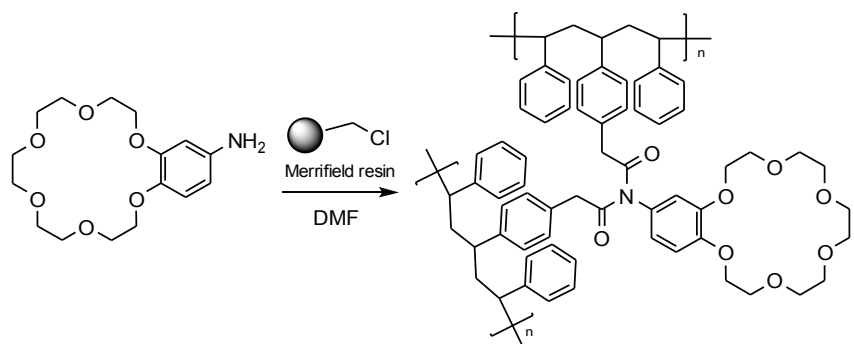
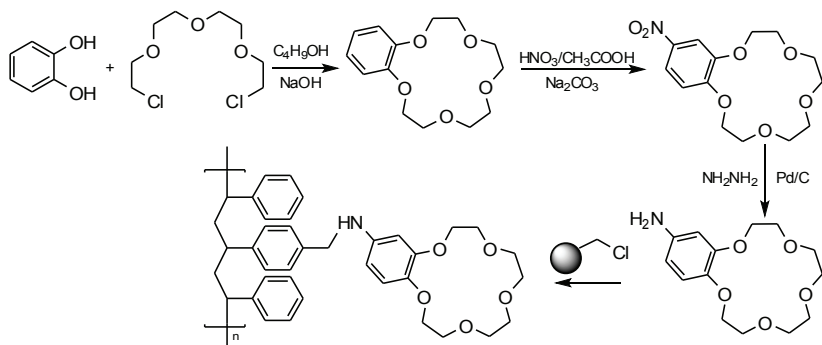Scheme 9. Synthesis of 4'-aminobenzo-18-crown-6 (AB18C6) bonded Merrifield's resin.

Both in two cases heavier isotope ^{7}Li was concentrated on modified resin, while the lighter isotope, ^{6}Li was concentrated in solution phase.

Scheme 10. Synthesis of 4'-aminobenzo-18-crown-6 (AB18C6) bonded Merrifield's resin.

A similar situation occurs in the case when, Merrifield's resin was modified by 1,13,16-Trioxa-4,7,10-triazacyclooctadecane (Scheme 11) [25]. The heavier isotope, $^7Li^+$, was enriched in the resin phase, while the lighter isotope, $^6Li^+$, was enriched in the solution phase.

In the case of ion exchange resins containing 2'-aminomethyl-18-crown-6 and 2'-aminomethyl-15-crown-5 bonded on Merrifield's resin occurr a reversible relationship in the case of using the magnesium ion. The heavier isotopes of magnesium were enriched in the solution phase, while the lighter isotopes were enriched in the resin phase [26-27].

Merrifield's resins among the many practical applications also found use as a medium in many reaction. Styring [28] reported the use of a new non-symmetric nickel(II) catalyst covalently bound to a Merrifield resin through a single point of attachment as an efficient catalyst for the Tamao–Kumada–Corriu reaction (reaction of formation the carbon–carbon bonds).The Tamao–Kumada–Corriu reaction has the advantage over Suzuki reaction [29] in that hybridizations of carbon other than sp2 can be utilised in the organometallic reagent. The reaction involves the oxidative addition of an organobromide to a transition metal catalyst, which then reacts with the organometallic Grignard reagent to give the coupled product by reductive elimination (Scheme 12). Additionally advantage of this reaction is a temperature factor. It can be carried out over a wide range of temperatures from−20 ºC to refluxing solvents, however for commercial efficiency a room temperature reaction is preferable. The nature of the immobilised catalyst means that it is easily prepared,

recovered and recycled. Furthermore, the supported catalyst lends itself to high throughput solution phase chemistry, in particular in the production of pharmaceuticals and fine chemicals because the products are free from transition metal contamination.
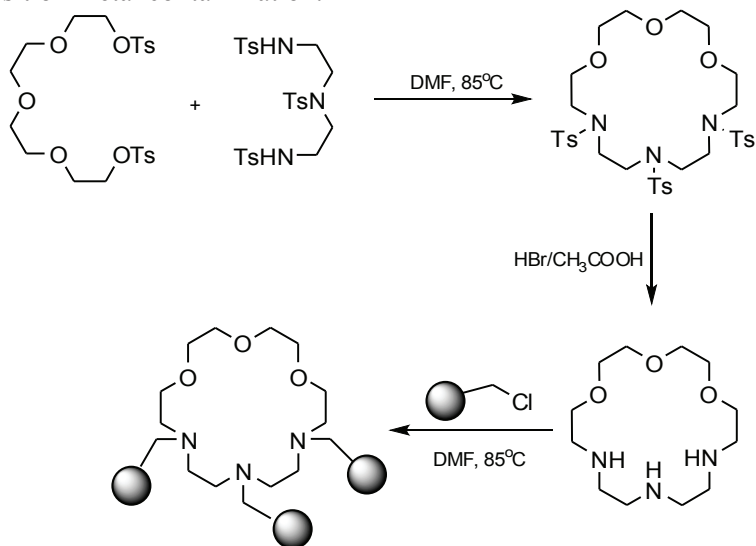

Scheme 11. Synthesis of 1,13,16-Trioxa-4,7,10-triazacyclooctadecane (TOTA) bonded Merrifield's resin.
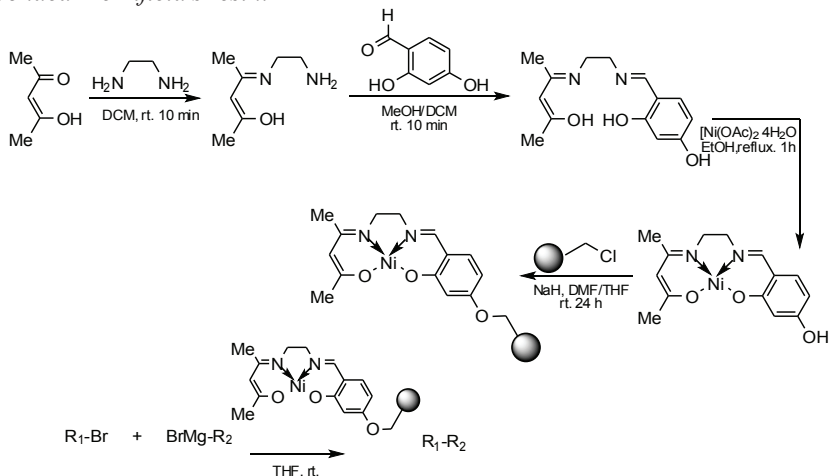
Scheme 12. Synthesis of the catalyst complex and its immobilisation on a Merrifield resin.

Although Merrifield resin is the foundation of many popular resins, incomplete coupling of the substrate can lead to unreacted chloromethyl sites on the resin. Such unreacted sites can interfere with the other substrates along the further phases of synthesis. Through the use of hydroxymethyl polystyrene it is possible to obtain chlorine free resin. In the case of this resin substrates are attached to the resin by reaction of an electrophile, such as an activated carboxylic acid, with the resin or by Mitsunobu reactions[30]. Unreacted core sites are usually acetylated by reaction with excess acetic anhydride in pyridine.

Basso [31] used SPOS to synthesis poly aryl-ether dendrimer attached on hydroxymethyl polystyrene resin (Scheme 13). This synthetic methodology is very useful and convenient because intermediates resulting in the synthesis doesn't require purify and the final products are very clean. The presence of a phenolic group and of two acetyl-protected primary alcohols allowed the synthesis of the dendrimer *via* a two-step iterative procedure, consisting of a Mitsunobu condensation followed by ester hydrolysis. To prove the versatility of this new resin, methyl 4-hydroxybenzoate was coupled *via* a Mitsunobu condensation onto resin and the resin-bound methyl ester was then reduced with LiAlH4. The synthesis of this dendrimer involved 7 distinct Mitsunobu condensations and14 distinct ester hydrolyses. The final loading was 86% of that expected this implies that each reaction had proceeded to 99.3% completion.

Scheme 13. The method of synthesis aryl-ether dendrimers on the hydroxymethyl polystyrene resin using Mitsonobu reaction.

Besides hydroxymethyl polystyrene resins, there are widely used aminomethyl (AM) resins, which are prepared by direct aminomethylation of polystyrene. This process gives a highly homogeneous and chemically defined support free from potentially reactive chloromethyl groups. Aminomethyl (AM) resin has long been used in solid phase peptide synthesis as a core resin to which various linkers could be attached through a stable amide bond.

Another amino resins such as benzhydrylamine (BHA) [32] and 4-methylbenzhydrylamine (MBHA) resins are still in use, despite of they have been originally developed for the formation of peptide amides using the Boc strategy. These types of resins are generally produced by electrophilic substitution of aromatic ring (Scheme 14). These resins form very stable amide or amine linkages to either carboxylic or electrophilic alkyl substrates, that is why very strong conditions are required to cleave substrates from these resins, therefore they are also used as base resins for anchoring linkers.
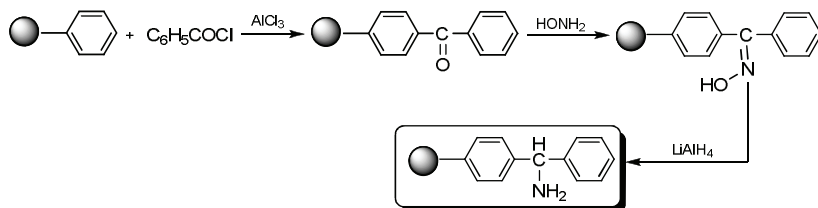
Scheme 14. The methodology of synthesis benzhydrylamine resin.

Bonnat [33] used the aminomethyl resin for the synthesis of a "tweezer" receptor specifically for peptides based on guanidinium group as the carboxylate binding site which formed a complex with a complementary peptidic guest in water. The guanidine unit was attached to Aminomethyl polystyrene resin via an arylsulphonamide, allowing cleavage from the resin with strong acid. The end of mono-tert-butyloxycarbonyl protected ethylene diamine was converted to the thiouronium salt in three steps via the isothiocyanate, in good overall yield and condensed with ammonia to give the diprotected guanidinium derivative (Scheme 14a).
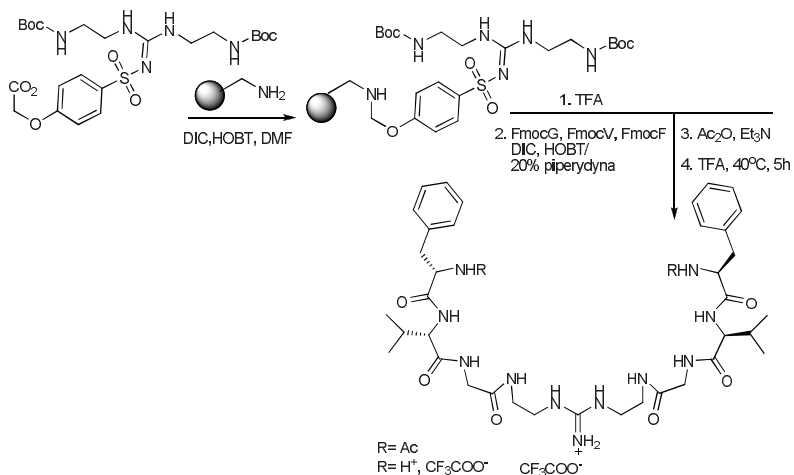
Scheme 14a. Synthesis of a "tweezer" receptor specifically for peptides based on guanidinium group.

Fioki [34] used aminomethyl polystyrene resin to the synthesis of chemosensitive library of fluorescence-labeled calix[4]arene substituted with peptides at the upper rim. The main aim of the created library was not only the selective binding the target pentapeptide (Leu^5 enkephalin) by the host molecules but also acting the role as chemosensors for the target. The sensors are consisting of two armed tripeptides directly attached to the aminomethylated calix[4]arene at the upper rim and pyrenyl groups attached to the N-terminal peptide, acting the indicating role. The change of fluorescence spectra is caused by conformational change of the peptidocalix[4]arene induced by the binding substrate.

The peptide sensors was created by the using of calyx[4] arene derivatives with two aminomethyl groups protected by Moz (p-methoxybenzyloxycarbonyl) and one carboxylic acid groups, which subsequently was condensed with aminomethylated polystyrene resin to prepare the peptide library on a solid suport. After removal of the N-Moz groups in a split synthesis was run on both sides of the arms to append a tripeptide using 15 Fmoc–amino acids as building blocks. Because 15 amino acids were used as building blocks, this library was consisted of $15^3 = 3375$ peptidocalixarenes. After removal of the N –terminal Fmoc group in the tripeptide, the library was condensed using 2-pyreneacetic

acid as a fluorophore. The protective groups on the side chain of peptides was removed by treating with trifluoroacetic acid (Scheme 15). Only a few beads of the whole library turned red with the interaction with the derivative of Leu[5] enkephalin marked by red dye. Consequently it turned out that 4 of 3375 library members were identified as the receptor for enkephalin, containing L-Tyr at AA_2 position and D-Phe in AA_3 position.
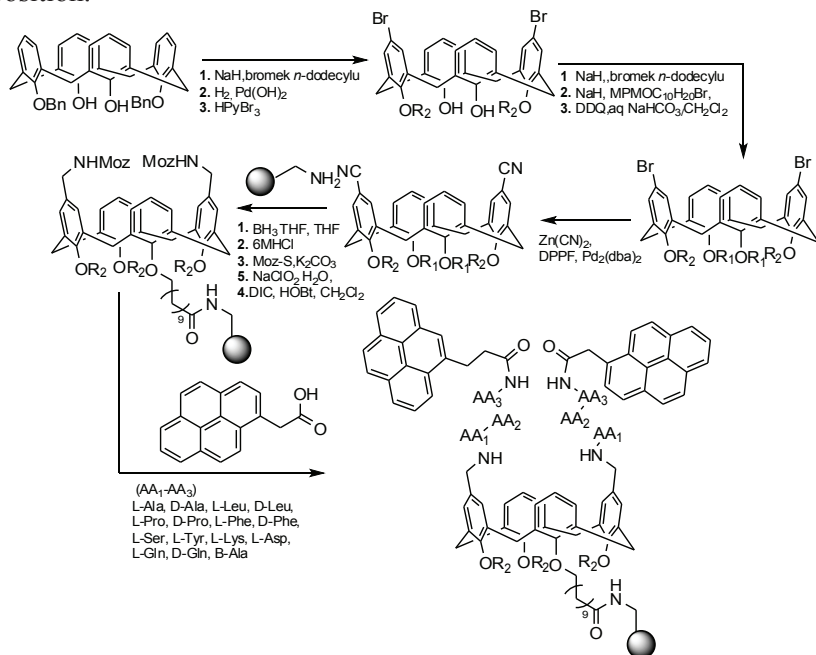
Scheme 15. Upper rim-modified peptidocalix[4]arene library.

The disadvantage of hydrophobic polystyrene resins is their lack of swelling in the protic solvents such as methanol and water, very often useful solvents for a numerous of organic reactions. Furthermore, the hydrophobic environment of the polymer matrix repels ionic species that are common organic intermediates.

Manufacturers of solid media to overcome of these problems, grafted onto the polystyrene core polyethyleneglycol (PEG), receiving a new type of resins commonly called TentaGel resin. The resulting resin has hydrophobic as well as hydrophilic character and swells well in solvents

such as in protic and aprotic solvents. As a result, resins TentaGel have found widespread use and application in a broader scope of chemistry. Additionally, substrates attached to the ends of the PEG tethers are less sterically hindered and have a greater freedom of movement that enhances reaction rates and improves the gel phase NMR spectra of support-bound substrates. Currently a wide choice of resins are available either in the electrophilic (Br), or nucleophilic (OH, NH_2 and SH) form, as well as derivatized with various linkers.

The advantages afforded by tile PEG graft are offset by the fact that the increased mass associated with the PEG, which comprises up to 70% of the bead mass, leads to a lower loading resin (-0.2-0.3 mmol/g) and the presence of the benzylic graft-polystyrene attachment results in instability to commonly used trifluoracetic acid cleavage conditions.

TentaGel resins found specific application in the supramolecular chemistry, especially in the synthesis of dendrimers, peptide receptors, sensors and metal complexes. These resins are widely used in Combinatorial Chemistry and Parallel Organic Synthesis. As a result of a lower loading of PEG resin the obtaining products are very obtained with purity.

Combinatorial chemistry can be efficiently used for the synthesis and evaluation of binding properties of libraries of synthetic receptors. This approach has been applied particularly to tweezer and other multi-armed receptors, and has been used for the identification of receptors for peptides in aqueous media, and for the development of new sensors and sensor arrays [35] what mostly is used in medicinal chemistry, to prepare large libraries of possible receptor structures, which could then be screened to identify a receptor for a given substrate.

The structure of such receptors generally consists of a scaffold or head group which is typically a conformationally restricted moiety that directs, or preorganises the functionalised substrate-binding arms. The combinatorial approach to these receptors proceeds by attachment of a suitably functionalized scaffold to a solid support, followed by library synthesis of the arms using a variety of monomer units and a split-and-mix approach (Figure 3). The arms may be synthesized simultaneously to give libraries of symmetrical receptors in which the arms are therefore identical in any given receptor, or they may be synthesized sequentially to give structurally more diverse libraries of unsymmetrical receptors.
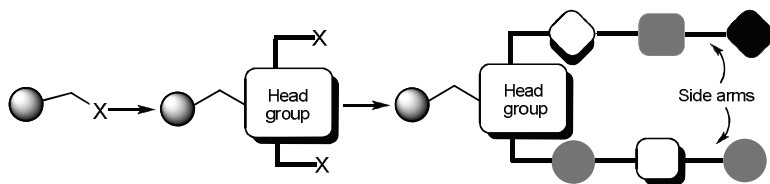
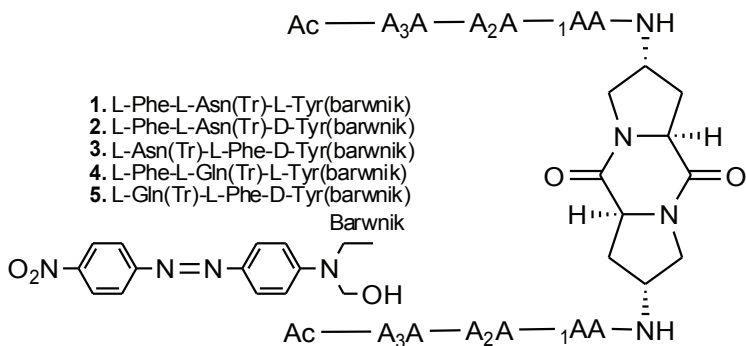*Figure 3. Combinatorial approach to tweezer receptors.*

The advantage of such receptors is that they are relatively easy to synthesize (in comparison with the macrocyclic structures) and, despite of their conformational flexibility, are clearly capable of selective recognition, both in organic and aqueous solvents. The use of amino acids as the monomer units for the construction of the receptor arms cause that it is easy to use them to the reactions on the solid-phase[35].

The selection of an appropriate skeleton is very important, because it depends largely on the arm side, which are responsible for the binding and molecular recognition.
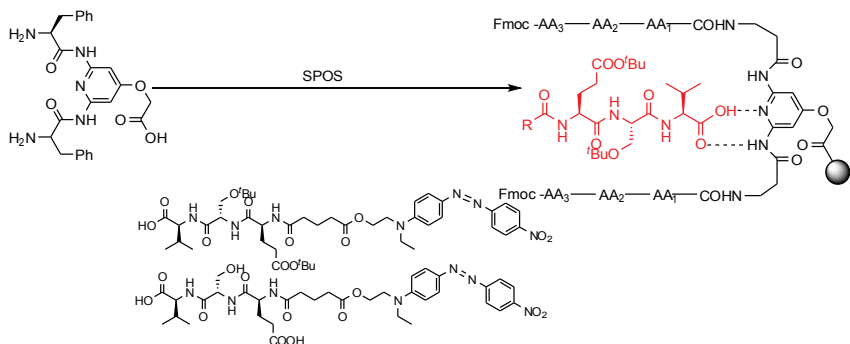
Conza [36] and co-workers shows synthesis and binding properties of two-armed receptors based on a diketopiperazine skeleton, containing a combination of three peptides in side-chain with dyemarked tyrosine (Scheme 16). The use of *trans-trans* diketopiperazine, with a rigid U-shaped conformation creates an ideal distance between the two branches, which affects the entire receptor binding properties. Structures derived from the more linear *cis-cis* diketopiperazine showed only moderately selectivity and no or moderate binding properties of the substrate.

In supramolecular chemistry occur receptors capable of binding selectively the specific substrate, in which the basic skeleton take an active part. Arienzo [37] described the synthesis and screening of libraries of tweezer receptors consisting of diamino pyridine carboxylic acid derivatives as a scleleton attached on the solid phase (Scheme 17). The diaminopyridine derivatives was attached to TentaGel resin, what allowed the use of combinatorial chemistry in order to find the most actively peptide sequence in the arm side.

Verification of the interaction between protected and free tripeptide markered with dye was made on library containing tripeptides in the arm side constructed of 12 amino acids which gave a $12^3 = 1728$ the total number of libraries.

1. L-Phe-L-Asn(Tr)-L-Tyr(barwnik)
2. L-Phe-L-Asn(Tr)-D-Tyr(barwnik)
3. L-Asn(Tr)-L-Phe-D-Tyr(barwnik)
4. L-Phe-L-Gln(Tr)-L-Tyr(barwnik)
5. L-Gln(Tr)-L-Phe-D-Tyr(barwnik)

*Scheme 16. Dye-marked diketopiperazine receptors.*

Scheme 17. Receptor containing the skeleton of diamino pyridine carboxylic acid derivatives, and dye labeled peptides using in the screening experiment.

The screening experiments with the protected day labeled peptide as a guest and with receptor library (Scheme 17) shown excellent selectivity for the four libraries containing in the position (AA_1) valine, in the position (AA_2) alanine or methionine, and in the position (AA_3) proline. For the unprotected peptide glutamine, alanine and methionie was found at the first position. Leucine and structurally very similar valine was found at the second position and at the third position alanine was found in each of five libraries in the tweezer side arm.

Schmuck and co-workers [38] using TentaGel resin have developed receptors for peptides with a carboxylate terminus group and have prepared libraries of peptides terminating with a guanidinocarbonyl pyrrole moiety, which serves as a carboxylate binding site (Scheme 18). The libraries

were prepared using standard Fmoc couplings. These structurally simple one-armed receptors were screened with dye-labelled L-Val-L-Val-L-Ile-L-Ala, C-terminal sequence of β- amyloid peptides, both in the polar and nonpolar environment. These peptides are responsible both in animals and humans for a variety of neuro degenerative diseases such as Creutzfeldt-Jakob or Alzheimer's disease. The name amyloid defines a group of amyloid peptides and proteins, usually glicolized, with commonly occurring peptide sequence. Schmuck's receptor library was based on the observation that the C-terminal sequence of Aβ (-Val[39]-Val[40]-Ile[41]-Ala[42]) is one of two domains being mainly responsible for its self-aggregation. It is thought to promote the formation of aggregated β-sheets stabilized through a combination of H-bonds and hydrophobic interactions [39]. In this receptors a tripeptide unit was chosen to provide the necessary binding sites for the formation of a hydrogen bonded antiparallel β-sheet with the backbone of the tetrapeptide substrate. To ensure strong complexation in polar solvents even for such a short β-sheet, a carboxylate binding site in the form of a cationic guanidiniocarbonyl pyrrole group was introduced.
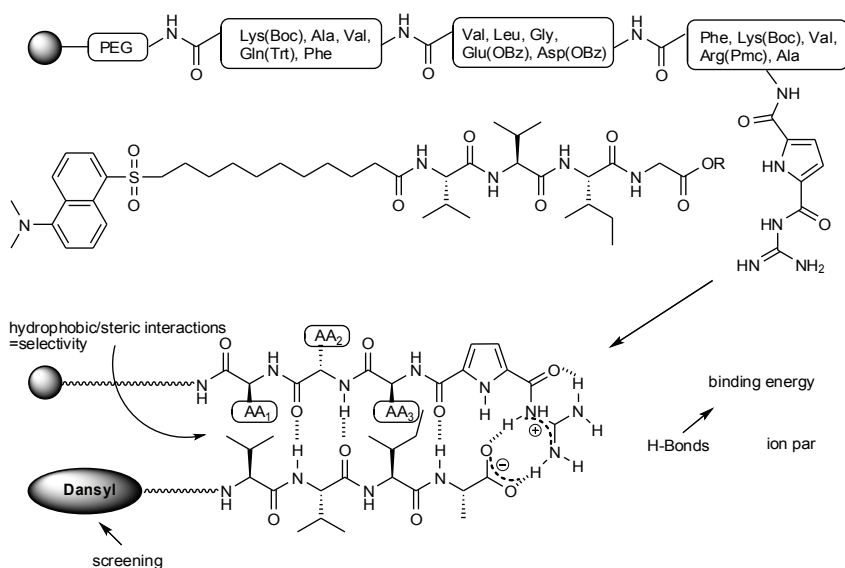
Scheme 18. A tripeptide-based library of cationic guanidiniocarbonyl pyrrole receptors of the general structure Amino-TentaGel-AA$_1$- AA$_2$-AA$_3$-Gua.(Gua guanidiniocarbonyl pyrrole cation) [38].

The binding properties of 125 different linear tripeptides receptors were synthesized on Amino-TentaGel and then studied in an on bead fluorescence binding assay For this purpose a fluorescence label in the form of a dansyl group was attached *via* a C11 alkyl spacer to the N-terminus of the tetrapeptide Val-Val-Ile-Ala. As a result 12 members of whole library, showed both strong (6 receptors) and weak binding (6 receptors) properties. The highest binding assay for the tetrapeptide showed the receptors containing Phe-Val-Val in a side arm.

The TentaGel resin have also found wide use in the synthesis of dendrimers. There are exist two main methods for the synthesis of dendrimers: a divergent approach, where the dendrimer is assembled in a totally linear manner, or a convergent method where fragments of the dendrimer are condensed together. These two methods both suffer from major problems when it comes to practical synthesis, in particular, the necessity for repeated and time-consuming purifications. The solidphase synthesis of dendrimers would have many advantages. Firstly, large excesses of reagents could be used without the problems usually associated with purification, which becomes only a matter of extensive washing. Secondly, the use of differently protected starter units would allow an avenue into the synthesis of unsymmetrical dendrimers under very clearly defined reaction conditions and allow the synthesized dendrimer to be specifically functionalized to other molecules of choice. The dendrimers generated using solid-phase techniques are much more homogeneous than those prepared using conventional solution methodology. [40].

Swali [40] synthesized two polyamidoamine (PAMAM) dendrimers on the solid phase starting from Tenta-Gel resin-bound linker. This acid-labile linker allows cleavage of the dendrimer from the resin when required for analytical control of dendrimer synthesis. The dendrimers was synthesized by repeated treatments of the resin with methyl acrylate and dirrerent diamines (Scheme 19).

The Tentagel resin have been used to synthesis sensors for alkali metal ions immobilized on solid phase. Nath [41] showed the synthesis of a cation receptor consisting of binding part (1-aza-18-crown-6), fluorophore unit (pyrene) and cholic acid immobilized on TentaGel resin (Scheme 20). The fluorescence of such a sensor beads is enhanced upon binding the cations especially in upon the addition of K^+ both in polar and nonpolar and solvents.
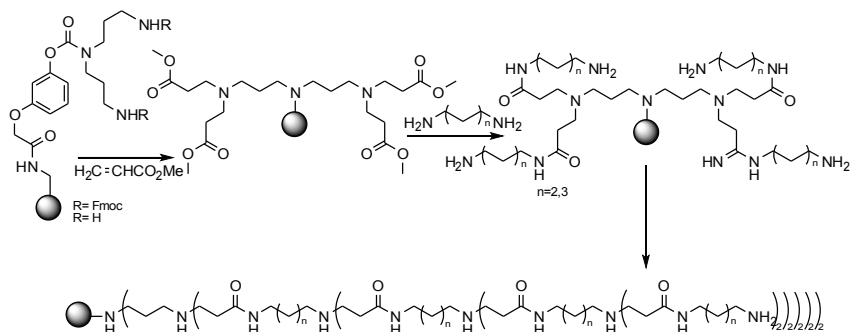
Scheme 19. Solid-Phase Synthesis of PAMAM Dendrimers with using Tentagel resin.
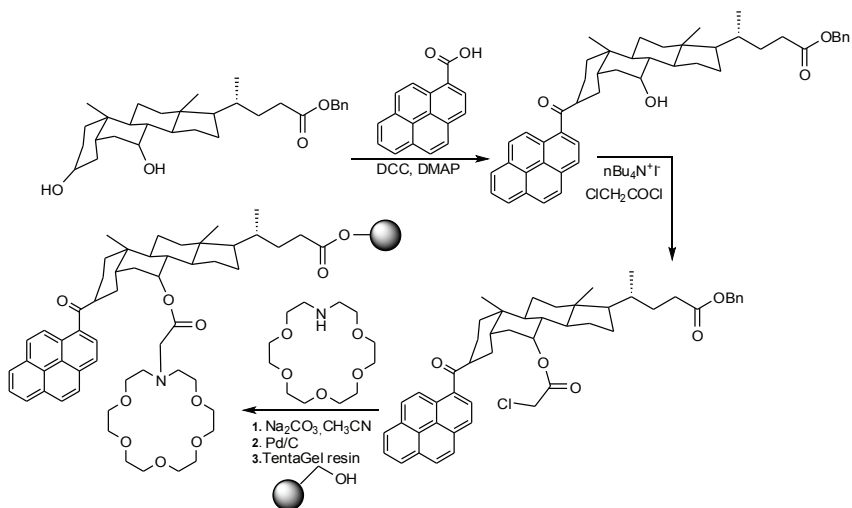
Scheme 20. Synthesis of the Sensor Beads

Brigo [42] used the TentaGel resin to covalently attachment solid phase the pH sensitive azo-dye and the construction of a PDMS/glass hybrid microfluidic cell for studying acid–base and time-response of the bead sensor by UV–vis microspectrophotometry under flow conditions. The resulting sensor change colors in different value of pH. At the pH5 the beads are yellow, besides at the pH 12 purple.
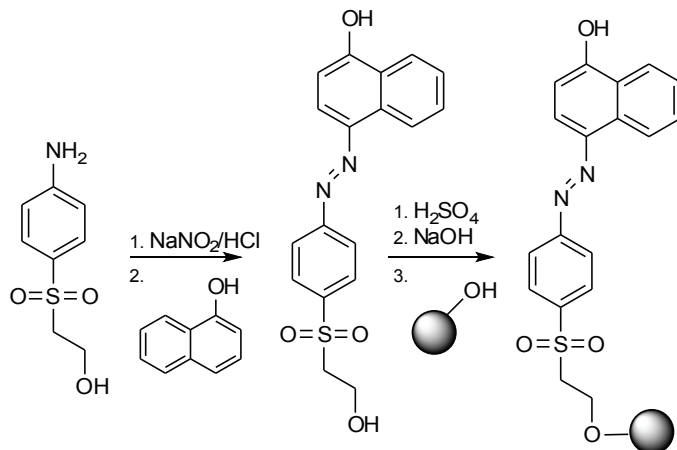
Scheme 21. Synthesis of a pH sensitive dye and its covalent attachment to TentaGel resin beads.

Solid phase synthesis found many application in coordination chemistry especially in the synthesis of ruthenium(II) complexes. Mulcahy [43] used the TentaGel resin to the synthesis of tris heteroleptic ruthenium(II) polypyridyl complexes on solid phase. After immobilized of 1,10-phenanthroline-5-carboxylic acid on a solid support, the resin was treated by $[Ru(bpy)(CH_3CN)_2Cl_2]/[Ru(bpy)(CH_3-CN)_3Cl]Cl$ (2,2′-bipyridine) and heated for 3 h at 80 °C to form ruthenium complex. Subsequently, the 4,4′-dimethoxy-2,2′-bipyridine was added to the resin and heated to 80 °C to form the tris-heteroleptic ruthenium complex apparent from luminescence of the beads upon exposure to UV light (Scheme 22). This method allow to obtain in a simple way with a high purity complexes of ruthenium without any significant amounts of side products.

Acetylated Polystyrene resins is another group of resins very often used in SPOS. They can be used as supports in solid phase synthesis or as scavenger resins in solution phase chemistry. These resins have acyl functional groups bound directly to the polymer core. The most frequently used resins are formyl polystyrene resin which can be used for solid phase syntheses, or as a support in a novel preparation of substituted furans [44] (Scheme 23).
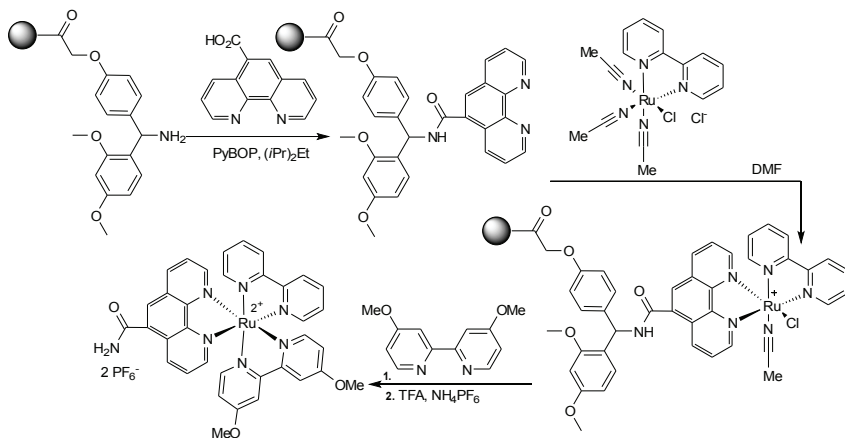
Scheme 22. Solid-Phase Synthesis of a tris-heteroleptic tuthenium(II) complex.
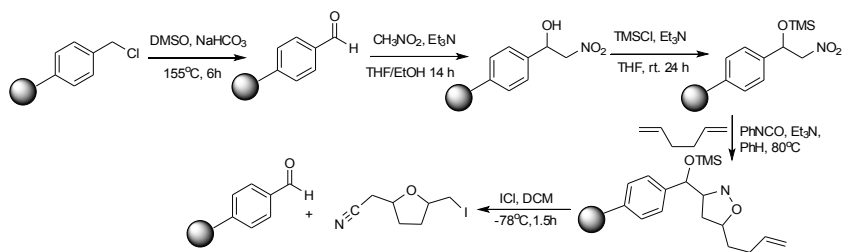
Scheme 23. Synthesis of 2,5-disubstitute tetrahydrofurans on polymer-support.

Formylpolystyrene resins are used to prepare other solid phase synthesis resins. Another acetyl-polystyrene resins are used as a scavengers in solution phase to remove the excess of hydrazines and alkyldithiols. Carboxypolystyrene resins are widely used as a solid phase support for alcohols and phenols [45].This resin can also be used to remove basic impurities from solutions.

PAM resin (4-Hydroxymethyl-phenylacetamidomethyl resin) is the most widely used resin in Boc chemistry peptide synthesis. It has greater acid stability than Merrifield resin. This resin is widely used in the synthesis of both long and short peptides. One of the many examples of use of this resin may is a synthesis of Abbenante [46], who has used the PAM resin for the synthesis of cyclic octapeptides capable of binding copper and potassium ions (Scheme 24).
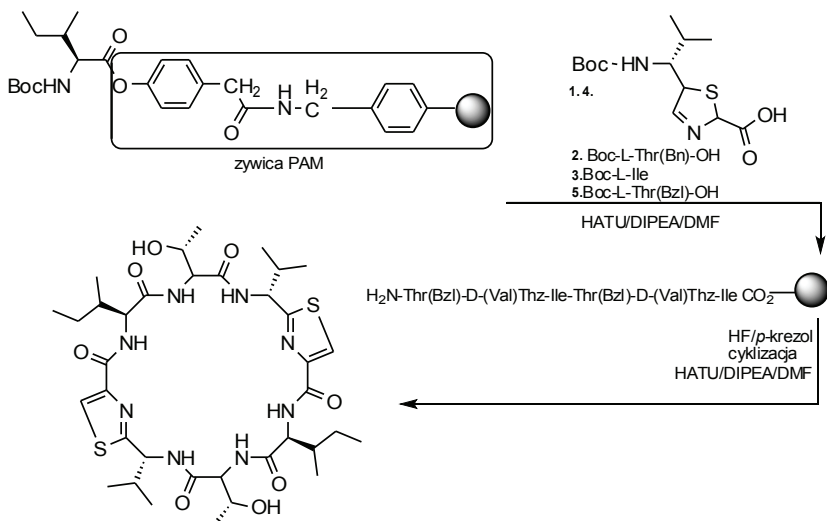
Scheme 24. Sznthesis of Cyclic Octapeptides.

The most widely used support for solid phase for acid substrates is the Wang resin, where to the polystyrene core is attached a 4-hydroxybenzyl alcohol moiety as a linker [47]. The linker is bound to the resin through a phenyl ether bond and the substrate is generally attached to the linker by a benzylic ester or ether bond. This linkage has good stability to a variety of reaction conditions, but can be readily cleaved by moderate treatment with an acid, generally trifluoroacetic acid. During synthesis impurities can form if a portion of the linker is attached to the resin through the benzylic position leaving a reactive phenolic site. This can occur during attachment of the linker if exact reaction conditions are not maintained [10].

Addition of the substrate is generally accomplished by coupling the nucleophilic resin with a desired electrophile or by a Mitsunobu reaction[30] Care should be taken when loading optically active substrates, such as -amino acid derivatives, because the activation step can lead to racemization. Novadays many techniques have been developed to minimize this problem.

Wang resins are available in electrophilic forms, such as benzyloxybenzyl bromide resin and the carbonate resins with succinimidyl, 4-nitrophenyl or imidazole as leaving groups. Benzyloxybenzyl bromide

resin is useful in forming simple benzylic linkages to substrates which are cleavable under acidic conditions. It can be especially useful with optically active acid substrates, such as _-amino acid derivatives, for the substrate can be attached to the resin without racemization [10].

Most polymers used for solid-phase synthesis based on cross-linked polystyrene beads originating from peptide and oligonucleotide chemistry are used in many types of reactions in organic chemistry. Revell has used the Wang resin to the cross-coupling reaction Suzuki-Miyaura (Scheme 25) applaying ionic liquids which promote various transition metal-catalyzed reactions in the both solid and liquid phase in room-temperature. Revell [48] showed the Suzuki-Miyaura cross coupling reaction of 4-iodophenol immobilized on solid phase with various arylboronic acids which was significantly accelerated by the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate (Scheme 25).
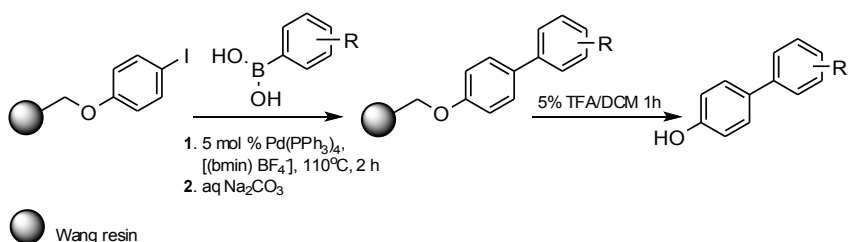
Scheme 25. Ionic liquid-accelerated Suzuki-Miyaura reactions of immobilized 4-iodophenol.

Chiang [49] modified the Wang resin with copper (II) derivative in order to obtain on its surface an effective catalyst, which has used in effective cross-coupling reactions between between N- or O-containing substrates and arylboronic acids. The copper catalyst is air stable and can be recycled with minimal loss of activity.

The mechanism of the reaction below (Scheme 26) is based on the coordination of the phenol/amine and oxidation by oxygen what gives a copper(III) intermediate. Transmetalation of intermediate product with the arylboronic acid gives product, which undergoes reductive elimination to expected main product and also provides the copper(I)-bound catalyst. The solid-phase catalyst can be recycled with minimal loss of activity and was able to promote the reaction catalytically.
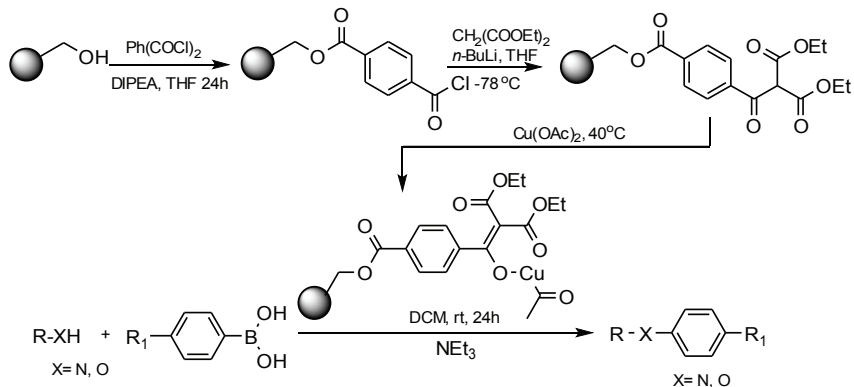
Scheme 26. Synthesis of the solid-phase copper catalyst.

Rivero [50] and co-workers used the Wang resin for synthesis of supramolecular systems based on the conception three-module format, "lumophore-spacer-receptor", synthesized the library on solid supports of 20 derivatives of 1,4,10,13-tetraoxa-7,15-diaza-cycloctadecane carrying a fluorescent dansyl group (Scheme 27). The use of supramolecular host-guest interactions may provide the basic recognition function acting as electron donor and the fluorophore playing the role of an acceptor.

Interaction between the receptor subunit and the luminescent moiety in such a way couse the light emission quenched or revived upon the recognition event. The luminescent mechanism that has yielded the greatest harvest so far for sensing applications is photoinduced electron transfer (PET). The Immobilization of fluorescent chemosensors on solid supports improve analytical properties, such as continuous readout, increase sensitivity, lower reagent consumption, and thepossibility of using the sensor in solvents in which the freemolecule may display low solubility.

The sensing fluorescence behavior of these materials (Scheme 27) toward alkali and alkali earth metal ions was studied by packing the beads into a conventional flow-through cell in a FIA (flow injection analysis) approach. The fluorescence emission of these materials responses shows a fluorescence increase to Li^+, Na^+, K^+, NH_4^+, Ca^{2+}, and Mg^{2+} with maximum sensitivity for Mg^{2+} over the rest of the ions.
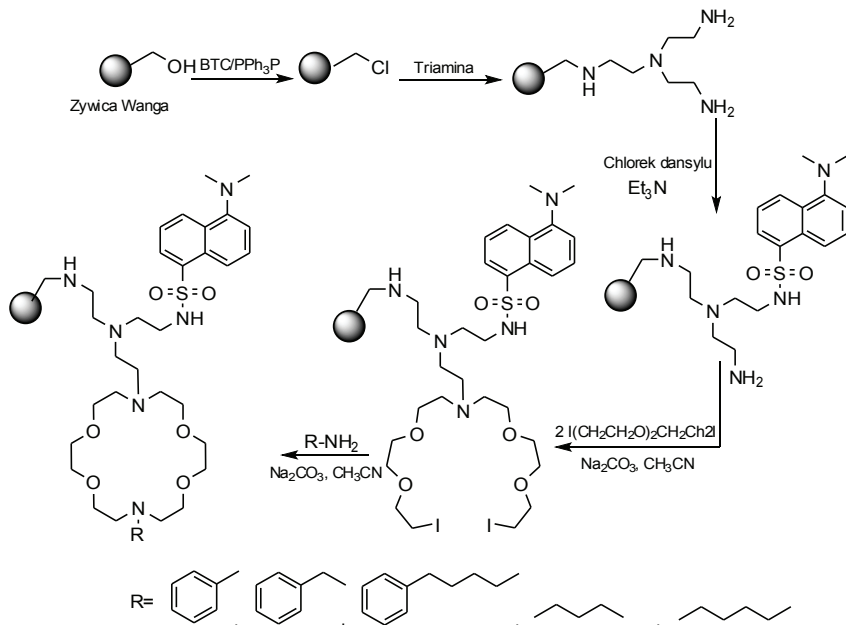
Scheme 27 . Synthesis of the derivatives of 20 derivatives of 1,4,10,13-tetraoxa-7,15-diaza-cyclooctadecane immobilized on Wang resin.

Rodríguez [51] using the Wang, and also other resins such as amide resin, showed a very convenient method for the incorporation of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) in to a peptide chains (Scheme 28) using the strategy of peptide synthesis. A large number of DOTA-peptide conjugates are synthesized for the clinical applications. This applications generalny are related to the nuclear medicine applications. The metal complexes of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)-peptide conjugates are widely used as targeted imaging and therapeutic radiopharmaceuticals and MRI contrast agents.

Polystyrene resins are also very often used in the synthesis of dendrimers. Most frequently, the polyamidoamine (PAMAM) resin found the widest application in synthesis of dendrimers [52]. However,

presently Wang resin have found greater use in the synthesis dendrimeres particularly based on derivatives of amino acids and peptides. Sanclimens [53] show the synthesis of protein globular dendrimers, derived from a combination of proline, glycine and imidazolidin ring as branching unit (Scheme 29). This methodology allows the synthesis of novel peptide dendrimers up to fourth generation using convergent solid-phase peptide synthesis. The conformational properties of branched polyproline peptides and proline dendrimers studied by CD experiments showed the conformational plasticity of branched.
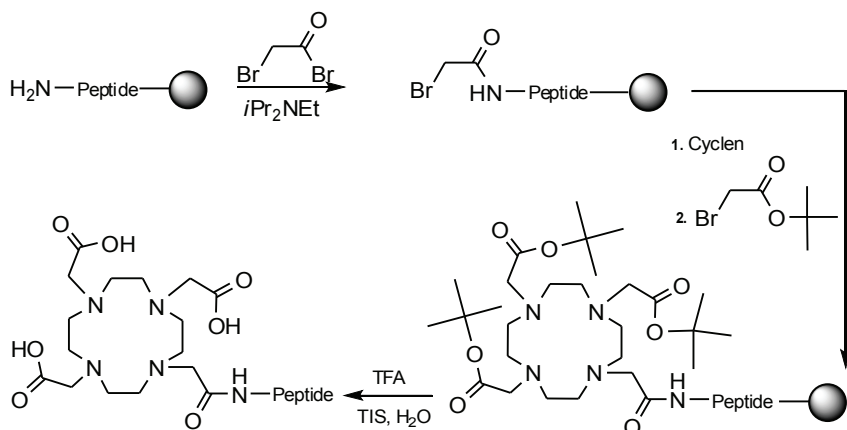
Scheme 28. Synthesis of DOTA derivatives Rusing solid phase synthesis.

In the solid phase synthesis (SPOS), especially in the peptide synthesis, when the intended product have to be in the amide form the special amide resins are used. The most popular solid phase supports for the formation of amide products include Rink, Knorr and PAL resins. All of these resins were originally developed for peptide amide synthesis using the Fmoc strategy. These resins are favored due to their higher acid lability. Cleavage can be performed under conditions as mild as 1% TFA. In solid phase organic chemistry, these resins have be used to produce amines by reductive alkylation. The acids can be coupled to this resins using standard amide forming conditions such as DIC/HOBt, HBTU or BOP.
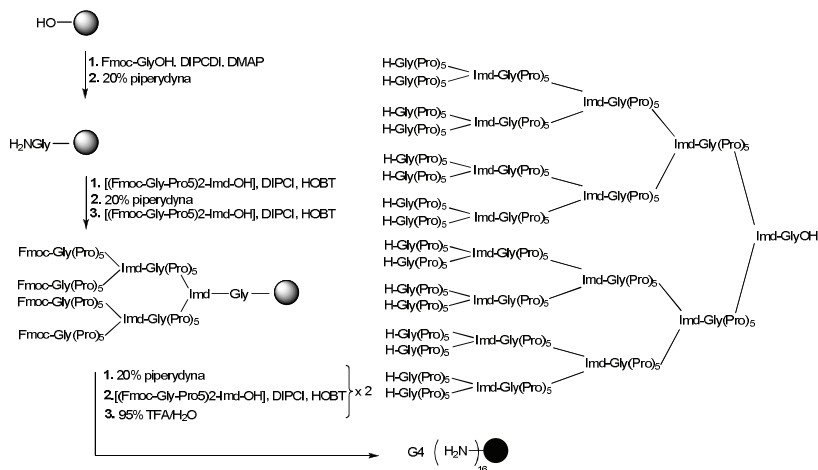
Scheme 29. General Strategy for the Synthesis of Proline Dendrimers.

Like in the case of Wang linker, the Rink linker is bonded to the polystyrene matrix through an ether linkage. Although the Knorr resin possesses the same functionality as Rink resin, the Knorr linker is bonded to the core through an amide linkage. Rink and Knorr resins exhibit similar characteristics with respect to cleavage conditions and the type of products formed. Rink resin, however, has been more widely utilized. PAL resin requires similar cleavage conditions to both Rink and Knorr resins, but it is somewhat more acid labile. PAL resin has been found to give cleaner products with long peptide sequences [10]. The most common resins of this type are used in supramolecular chemistry to the synthesis of peptides, cyclic peptide [54] glycopeptides and receptors for other peptides [55].

The Trityl resins have been widely used in both solid phase organic and peptide chemistry. These resins are very acid labile and can even be cleaved with acetic acid. These resins are particularly useful when less acid labile protecting groups are required on the substrate following cleavage, or in cases where the substrate can cyclize on the anchoring linkage causing premature cleavage. The bulky triphenylmethyl group prevents such attack through steric hindrance. The trityl and 2-chlorotrityl resins are available in either the alcohol form or the chloride form. The chloride form is exceedingly moisture sensitive and must be handled and

stored under inert conditions.

Kenichi [56] performed macrocyclization reaction on a solid support using the Heck reaction. The reaction of cyclization from the head to the tail on a solid support was performed by linear precursor anchored to a 2-chlorotrityl chloride resin via an ester linkage using the β-carboxyl group of Asp. The Heck coupling of acrylic acid amide to 3-iodobenzylamine on the solid support proceeds smoothly to yield a cyclic tetrapeptides derivatives, contained 3-substituted cinnamic acid template and Arg-Gly-Asp sequence. The macrocyclization reaction take place more rapidly on a solid support than in solution. This reaction in a solution is unenforceable, or difficult to achieve.
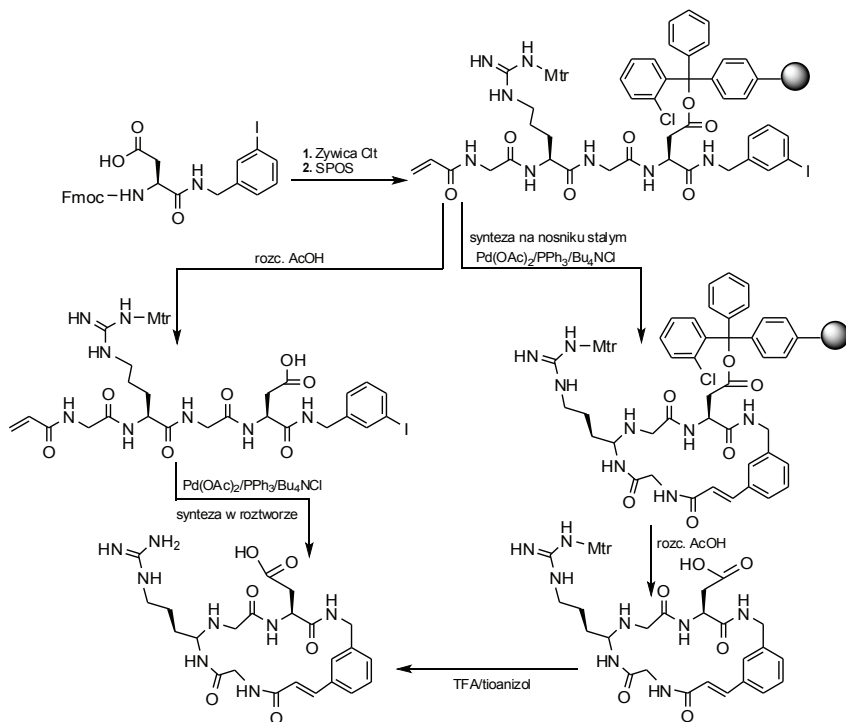

Scheme 30. Synthesis of cyclic tetrapeptides with using of 2-chlorotrityl resin.

In addition the trityl resins is used to immobilize acids, alcohols, or thiols on solid phase. This allow to obtain new compounds with

free carboxylic acid, alcohol or thiol group. Mourtas [57] attached mercapto acids through their thiol group onto various resins such as: 2-chlorotrityl (Clt)-, trityl (Trt)-, 4-methyltrityl (Mtt)-, 4-methoxytrityl (Mmt)- and 4,4-dimethoxytrityl (Dmt)-resins (Scheme 31). These resins the 4-methyltrityl and 4-methoxytrityl resins are more labile than trityl resin.

This new resins were used in the solid-phase synthesis to obtain mercaptoacyl aminoacids which are very important from biological point of view, because they are inhibitors of metallopeptidases. The cleavage of the mercapto acids from the various resins was performed by treatment with TFA solutions.
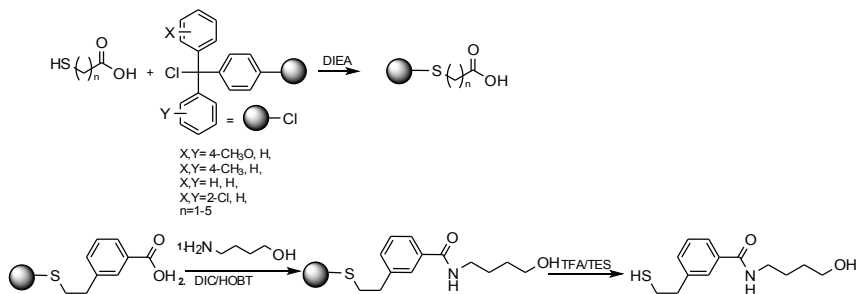

Scheme 31. Synthesis of mercapto acids from the various resins.

The substituted 2-chlorotrityl resin have found wide application to form and synthesis the amide bond. Meller [58] using the N-Fmoc-hydroxylamine generated a facile route to a high loading, acid labile novel N-Fmoc-aminooxy-2chlorobityl polystyrene resin bearing a hydroxylamine linker (Scheme 32). This resin is very useful for the construction of hydroxamic acids, including peptidyl hydroxamic acids. Hydroxamic acids are a potent enzyme inhibitors and are potential therapeutic agents.

Very often in the solid phase synthesis (SPOS) and peptide chemistry the resin labile in alkaline conditions are also used. To this type belong (MBHA) resin containing 4-methylbenzhydrylamine linker and (HMBA-MBHA resin) containing 4-hydroxymethylbenzoyl linker. The amide bonds formed on this resins can be cleaved very easy that is why they are the most used resins in the synthesis of amide. The products from this resins can be cleaved with a variety of nucleophilic agent and the

form of products depends on of the applied agent. Ammonia or primary amines gives amides [59], hydrazine gives hydrazides [60], methanol/triethylamine gives methyl esters [61], sodium borohydride gives alcohols.
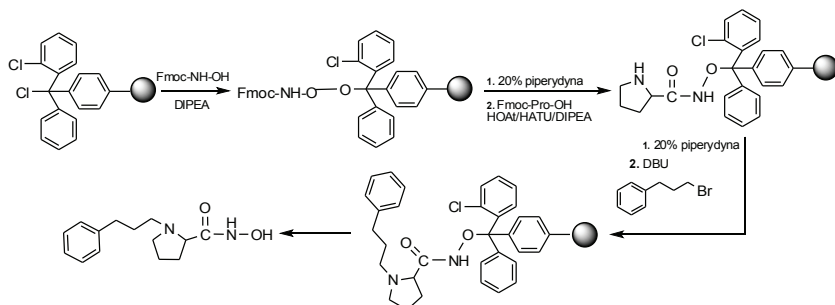
Scheme 32. Synthesis of hydroxamic acids based on 2-chlorotrityl resin.

Summary

Synthesis on the solid phase synthesis (SPOS) is a very useful and convenient method of synthetic, which is currently used not only in peptide chemistry, for which was originally created, but came after a peptide laboratories and has become indispensable method adapted for the needs of all organic laboratories. For the Supramolecular Chemistry, the fields of science archiving in the last two decades the great scientific flourishing, the method of solid phase synthesis has become very grateful and often used in the synthesis of supramolecular systems .As a result of high demand for resins for solid phase synthesis, not only the chemical industry was developed but the sector responsible for the production and distribution of resins. The researchers should know to plan the every synthesis exactly by choosing the appropriate synthesis strategy and the suitable kind of resin.

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Chapter 4

Intramolecular interactions in *ortho*–(aminomethyl) phenylboronic acids – potent saccharide receptors

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Arylboronic acids are systems that attract an increasing scientific interest due to their new applications in organic synthesis, catalysis, supramolecular chemistry, biology, medicine and material engineering [1]. Their unique feature of forming reversible covalent complexes with sugars has been applied in the construction of new saccharide sensors, creating a possibility of designing a sensor for each sugar, including enantiomers [2].

Fluorescent receptors are the most important ones from the point of view of their applications. Fluorescent method of detection is fast (sub-milisecond response time is typical), cheap (low-cost lasers or even LED systems) and sensitive (typical concentration of 10^{-6} M).

One of the most important fluorescent sensors are arylboronic acids with the aminomethyl group in ortho position (**I**). This type of compounds were described as early as in 1982 by Wulff [3] and are called as "Wulff-type systems" or "1–5 systems" according to atoms arrangement.

The mechanism for the receptor activity for this type of compounds was proposed by James et al. [4] (scheme 1).

Hence, intramolecular interactions in these compounds play a key role in the receptor activity of these compounds. Especially, formation of the dative N→B bond in resulting sugar ester is responsible for enhanced

binding constant. The aim of this work is to review crystal structures of *ortho*–(aminomethyl)phenylboronic acids and their derivatives (esters and anhydrides) to analyse the influence of substituents.
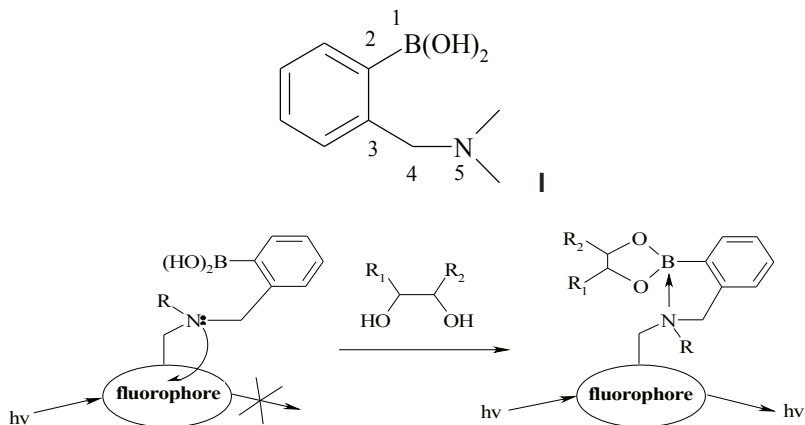
Scheme 1. Photoinduced electron transfer (PET) based on the interaction of boronic group with amino group.
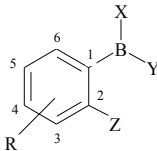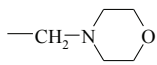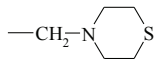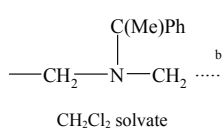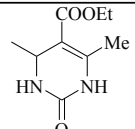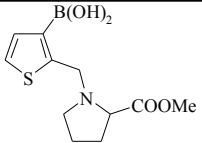
In Table 1 the structural data for *ortho*–(aminomethyl)phenylboronic acids and esters are collected. Analysis of the values of N···B and O–H···N distances allow to ascertain which kind of intramolecular interaction is observed (dative N→B or hydrogen B–O–H···N bond). The values of O–B–O angle give the information about the hybridization of the boron atom and on the strain caused by the formation of the cyclic esters.

Table 2 presents the data for the corresponding substituted boroxins. Determination of the N···B distances allows to answer the question on the formation of dative N→B bond for each boron centre in this molecule. These data are given for comparison: triorganoboroxins do not show sugar receptor activity, but due to the easy dehydration of boronic acids are often present as by-products in the reaction mixtures obtained in the synthesis of acids and esters.
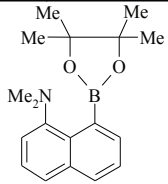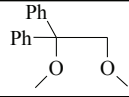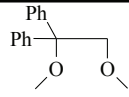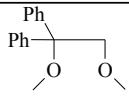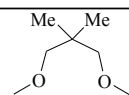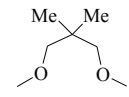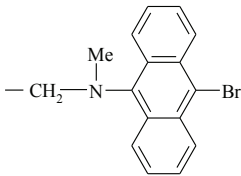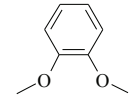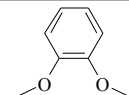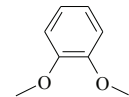
Table 1.
Selected bond length (Å) and bond angles (deg) of crystalline ortho–
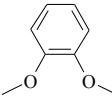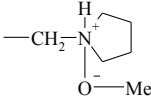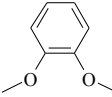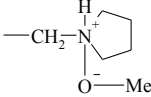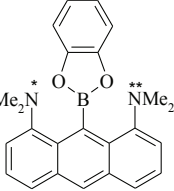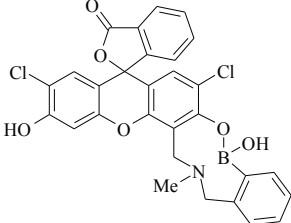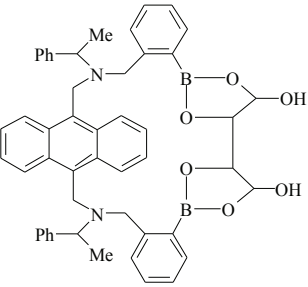
(aminomethyl)-phenylboronic acids and esters (**II**). The values of N···B or O–H···N distances for the cases where dative or hydrogen bonds are formed are underlined.

Entry	X, Y R (if other than H)	–Z	N···B or O–H···N distance	O–B–O angle	Ref. and CCDC code
1	OH, OH	–CH$_2$–N(iPr)$_2$	3.285 _2.637_	120.38	5 DECRIN
2	OH, OH R4=CF$_3$	–CH$_2$–N(iPr)$_2$	3.285 _2.623_	121.02	6
3	OH, OH R6=F	–CH$_2$–N(iPr)$_2$	3.287 _2.607_	120.42	6
4	OH, OH	—CH$_2$–N◯O	_2.659_ _2.606_ _2.611_	119.51 119.81 120.11	7
5	OH, OH	—CH$_2$–N◯S	_2.599_	119.51	7
6	OH, OH	–CH=N(OMe) [a]	3.141 _2.595_	118.63	8 YICHOH
7	OH, OH	—CH$_2$—N—CH$_2$ ····· [b] C(Me)Ph CH$_2$Cl$_2$ solvate	3.340 _2.748_ _2.759_ _2.764_ _2.776_	119.56 119.79 120.16 120.21	9 FAKTER
8	OH, OH	COOEt, Me, HN NH, O	3.526 _2.899_	117.49	10 XECHUJ
9	B(OH)$_2$ S ...N—COOMe		3.299 _2.671_	120.68	11
10	OMe, OMe	–CH$_2$–NH–CH$_2$Ph	_1.665_	114.87	11, 12 MADHEF
11	OMe, OMe	–CH$_2$–NH–CH$_2$–....[c]	_1.669_	114.81	13 QUDPAG
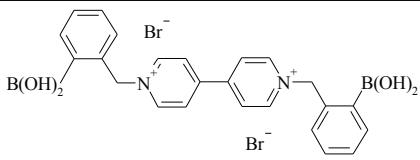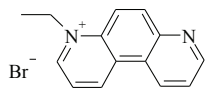
Entry	X, Y **R** (if other than H)	–Z	N···B or *O–H···N* distance	O–B–O angle	Ref. and CCDC code
12	OEt, OEt	—CH=N*—NH**—(2,4-dinitrophenyl, O_2N)–NO_2	2.721* 3.980**	119.34	14 LUKMAF
13	OEt, OEt **R4 = OMe**	—CH=N*—NH**—(2,4-dinitrophenyl, O_2N)–NO_2	2.750* 4.001**	118.96	14 LUKLUY
14	Me Me / Me—C—Me / O O (pinacol)	—CH_2–N(piperazine)N–pyrimidine	3.129	115.89	15 MIZGOR
15	Me Me / Me—C—Me / O O (pinacol)	–C(O)–N(iPr)$_2$	3.806 (B...O: 1.525)	113.68	5 DECRUZ
16	Me Me / Me—C—Me / O O (pinacol)	(imidazolidine: NH, HN—CH) THF solvate	1.683 1.685	105.31 105.56	16 OLIVIO
17	Me Me / Me—C—Me / O O (pinacol)	(imidazolidine: N–Ph, HN—CH)	1.681	106.80	16 OLIVEK
18	Me Me / Me—C—Me / O O (pinacol)	(Me Me imidazolidine: NH, HN—CH)	1.702	106.48	16 OLIVAG
19	Me Me / Me—C—Me / O O (pinacol)	(imidazolidine: N–$(CH_2)_2$N=CH–pyridine, HN—CH) Et$_2$O solvate	1.688 1.690 1.702	106.10 106.29 106.74 106.82	16 OLITUY
20	Me Me / Me—C—Me / O O (pinacol)	-CH_2=N-NH-C(O)–pyridyl–N	4.338 5.116	112.30	17 RERYUJ
21	Me Me / Me—C—Me / O O (pinacol)	–CN	3.833	113.22	18 ODERUL

Entry	X, Y R (if other than H)	–Z	N···B or O–H···N distance	O–B–O angle	Ref. and CCDC code
22	Me–C(Me)–O–B–O–C(Me)–Me with Me₂N on naphthalene		1.832 1.885	108.08 108.39	19 ALAGUP
23	Ph, Ph–C–C–O O (pinacol-type Ph)	–CH₂–NMe₂	1.754	107.21	20 KUSLAL
24	Ph, Ph–C–C–O O	–CMe₂–NMe₂	1.747	107.46	21 CUPBOE
25	Ph, Ph–C–C–O O **R6 = CH₂NMe₂**	–CH₂–NMe₂	1.762 (4.583 ^{d})	107.38	22, 23 ZOLSAU
26	Me, Me–C–O O	–CH₂–NMe₂	1.766	117.68	24
27	Me, Me–C–O O	—CH₂—N(Me)–anthracenyl–Br	3.204	123.20	25
28	catechol O O	–C(O)–NEt₂	^{e}		26 YUWPUB
29	catechol O O	–C(O)–N(iPr)₂ catechol solvate	3.593 (B...O: 1.556)	105.08	26 YUWPOV
30	catechol O O	—CH₂—N(pyrrolidine)	1.683 1.700	105.70 105.77	11

Entry	X, Y **R** (if other than H)	–Z	N···B or O–H···N distance	O–B–O angle	Ref. and CCDC code
31	(benzene ring with two OMe groups, 1,2-dimethoxy)	—CH₂—N⁺(H)(pyrrolidine), O⁻—Me	3.190 3.270 3.352 (O⁻···B: 1.462 1.478 1.485)	102.43 103.30 105.02	11
32	(benzene ring with two OMe groups)	—CH₂—N⁺(H)(pyrrolidine), O⁻—Me water solvate	3.403 (O⁻···B: 1.441)	101.14	11
33	Me₂N* ... NMe₂** (anthracene with catechol boronate)		1.809* 2.941**	107.53	27, 28 OGAPIV
34	(chlorinated fluorescein with benzoxaborole, HO, Cl, Cl, Me–N)		1.685	106.42	29 WESMEN
35	Ph(Me)CH–N–CH₂ ... (anthracene bis-boronate, Ph(Me)CH, OH, OH) methanol solvate		3.433 3.496	102.39 102.68	9 FAKTIV

Entry	X, Y R (if other than H)	–Z	N···B or O–H···N distance	O–B–O angle	Ref. and CCDC code
36			4.546 *4.210*	116.85	30 KEGNAM
37	OH, OMe		4.413	118.97	31 IROVOA

[a] *Positions of hydrogen not determined.*
[b] *Two boronic units form cyclic compound linked through the anthracene unit.*
[c] *Two boronic units linked through the ring sequence.*
[d] *N···B distance to the second CH$_2$NEt$_2$ group.*
[e] *Low-resolution structure; data not available in CCDC.*

Table 2. Selected bond length (Å) of crystalline tris(ortho–aminomethylphenyl) boroxins (**III**). The values of N...B distances for the cases where dative bond is formed are underlined.

Entry	R$_1$, R$_2$	Distances			Ref. and CCDC code
		N$_1$···B$_1$	N$_2$···B$_2$	N$_3$···B$_3$	
1	H, Ph	<u>1.747</u>	2.820	3.754	32 EWIDAP
2	Me, Me	<u>1.756</u>	<u>1.765</u>	3.170	24 MEXZEU
3	Me, Fc	<u>1.842</u>	<u>1.775</u>	<u>1.829</u>	24 MEXZAQ
4	CH-N=N*Me$_2$ [a]	<u>1.678</u>	<u>1.687</u>	5.237	33 TELQEG
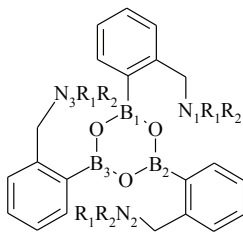
Entry	R$_1$, R$_2$	Distances			Ref. and CCDC code
		N$_1$···B$_1$	N$_2$···B$_2$	N$_3$···B$_3$	
5		<u>1.902</u>	<u>1.968</u>	<u>1.978</u>	19 ALAGOJ
6		<u>1.640</u>	<u>1.666</u>	3.836	34 KENBUB

a substituent in ortho-position of phenyl ring; N*···B distances given.

Analysing the structural parameters of the compounds presented in Table 1 one can conclude:

- In case of phenylboronic acids with aminomethyl group in *ortho* position intramolecular hydrogen bond is formed. O···N distance is about 2.6 Å (2.559 to 2.899 Å). The most typical dimeric structure is shown in Figure 1.
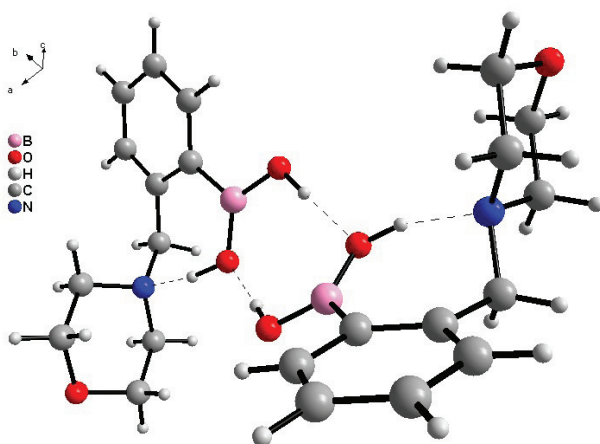
Figure 1. Dimer of ortho–substituted phenylboronic acid with inter- and intramolecular hydrogen bonds [7].

- In case of boronic esters the structure with dative intramolecular N→B bond is most common one (Figure 2).

(a)   (b)
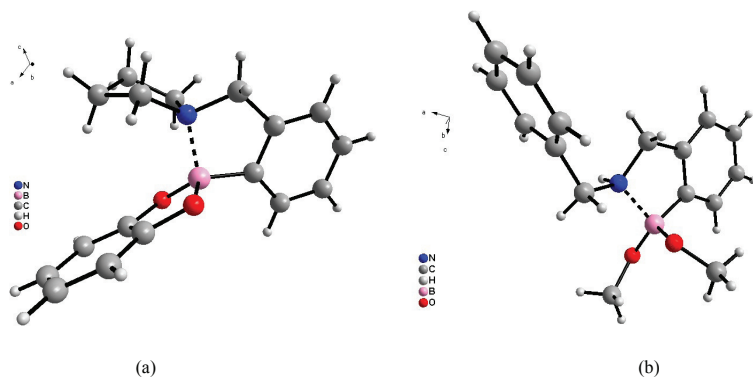
Figure 2. Intramolecularly coordinated boronic esters with cyclic (a) and linear (b) alcohols [11].

The N···B distance in these compounds is about 1.7 Å. In the compounds with amido group the dative O→B bond is formed instead of the N→B one as it is energetically favorable (length *ca*. 1.5 Å) (Figure 3).
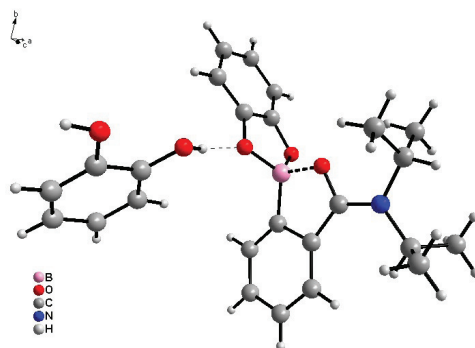
Figure 3. Intramolecular O→B interaction with amido substituent (additional catechol molecule coordinated by hydrogen bond) [26].

- In case of bulky substituents in aminomethyl group steric hindrance disables the formation of intramolecular dative bond (*e.g.* Table 1, entry 27). Unfavorable arrangement of the donor atoms can also cause the lack of intramolecular coordination (Figure 4).
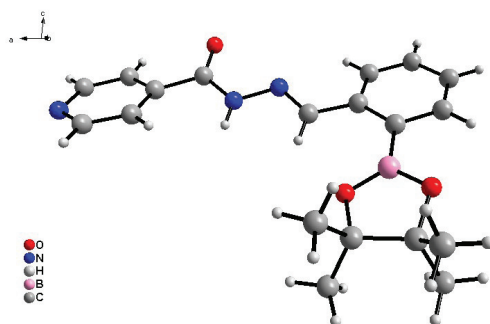
Figure 4. Boronic ester possessing three potential donor atoms in the group in ortho position, but without intramolecular coordination [17].

- Spacial arrangement of the boronic ester and amino group makes possible the intramolecular coordination for polycyclic compounds (Figure 5).
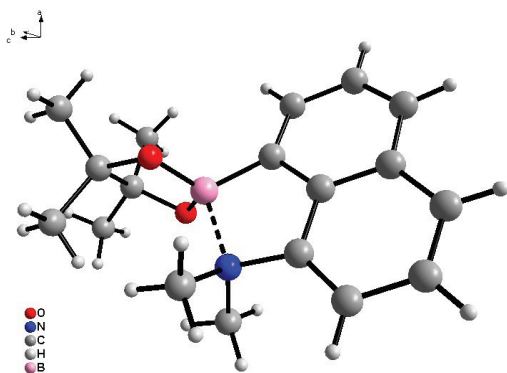
Figure 5. Intramolecular coordination for naphthalene derivative [19].

Examples presented above show that when hydrogen bond formation is possible, it is formed as energetically favorable. The influence of the solvent on the equilibrium in solution was discussed in [35]. The examples of intramolecularly coordinated solvent molecules were given by Anslyn *et al.* [11] (Figure 6).
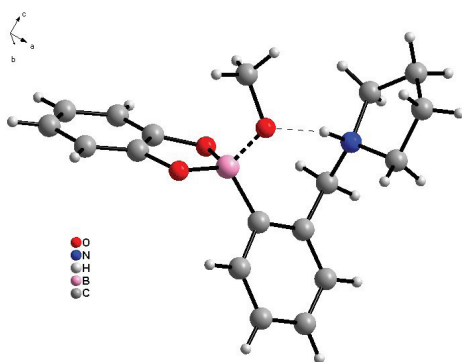
Figure 6. Intramolecularly coordinated molecule of methanol with hydrogen transfer to nitrogen atom [11].

- • For phenylboronic acids and esters with ternary nitrogen atoms in *ortho* position intramolecular interactions are not observed (Table 1, entry 36, 37). It is also the case for cyano group (entry 21).

  Formation of intramolecular dative bond is also observed for ortho–substituted boroxins (Table 2). Depending on the size and arrangement of the substituents, one, two, or three boron atoms can be intramolecularly coordinated (Figure 7).
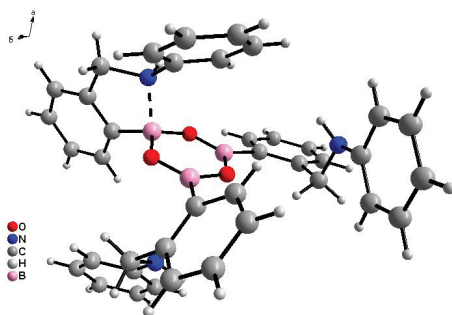
(a)
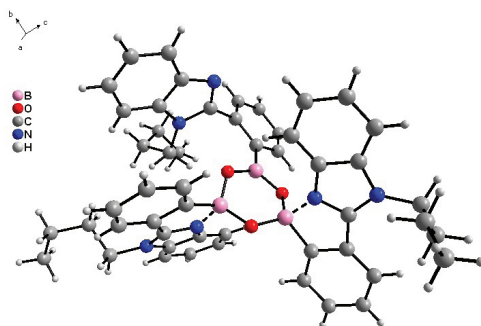
(b)
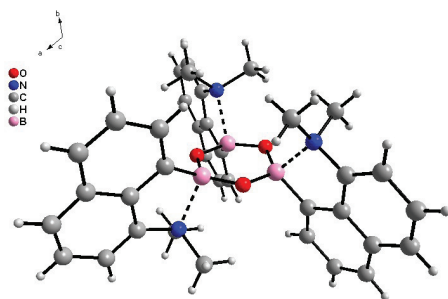
(c)

Figure 7. ortho-Aminomethyl subsituted triarylboroxins with one [32], two [34] or three [19] tetra–coordinate boron centers.

Formation of the ester and coordination of the boron atom changes the geometry on the boron center. For the boronic acids with intramolecular hydrogen bond, typical value of the O–B–O angle is about 120º. Formation of the ester without N→B bond formation do not affect this value for linear alcohols, and may decrease this value in case of the esters with 1,2–diols (Table 1, entry 20, 21). This compression of the angle can facilitate coordination of the boron atom, causing the observed increase in the value of the acidity constant of the ester compared to the acid. This subject is widely discussed in [2] (Chapter 3.2). The mean value of thi angle for sp^3 tetrahedral boronate is about 106º.

Acknowledgement

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Chapter 5

Synthesis of aminoacids and peptides with supramolecular substituent

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Biologically activated amino acids and peptides that are functionalized by aza- and crown ethers - the substituents with complexing abilities – form the new class of ionic receptors [1-4]. The functionalization of aminoacids through the complexing substituents of monovalent cations results in the receptor sensitivity to the ion concentration in the media, independently from pH value. The formed host-guest complex is characterized by different properties compared to initial chemical individuals. The selectivity of studied ionoreceptors determine size and type of crown ether as substitents in aminoacids. However, another reaction – the protonation of basic centres – is competitive compared to the complexation. Each process – the complexation and the protonation – gives an ionic character of systems studied. The main difference between those processes consists in chemical bonding formation in the protonation one, while the host-guest complex is formed through incovalent interaction of metal ions and free electron pairs of crown ether oxygen and nitrogen atoms. For all studied molecules it is observed in ESI mass spectra two concurred processes: protonated and complexation. The signals of protonated forms disappear and signals of complexation forms increase with rise of value of cone voltage. Fig. 1 shown the ESI mass spectra of acetonitrile solution containing (1-(1-antraquinoyl)-7-(carboxymethyl)-1,7-diaza-12-crown-4) and mixture of metal monovalent ions.
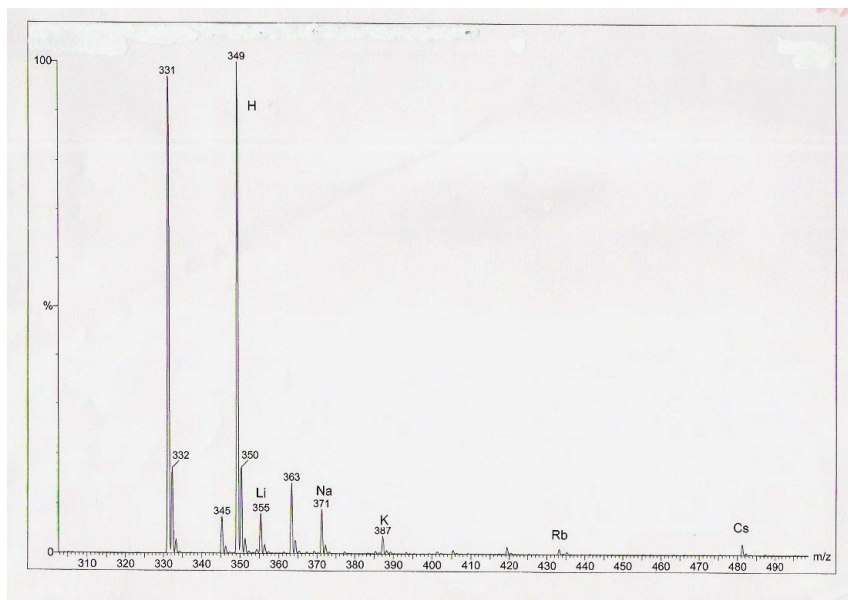
Figure 1. ESI mass spectra of acetonitrile solution containing (1-(1-antraquinoyl)-7-(carboxymethyl)-1,7-diaza-12-crown-4 and mixture of metal monovalent ions.
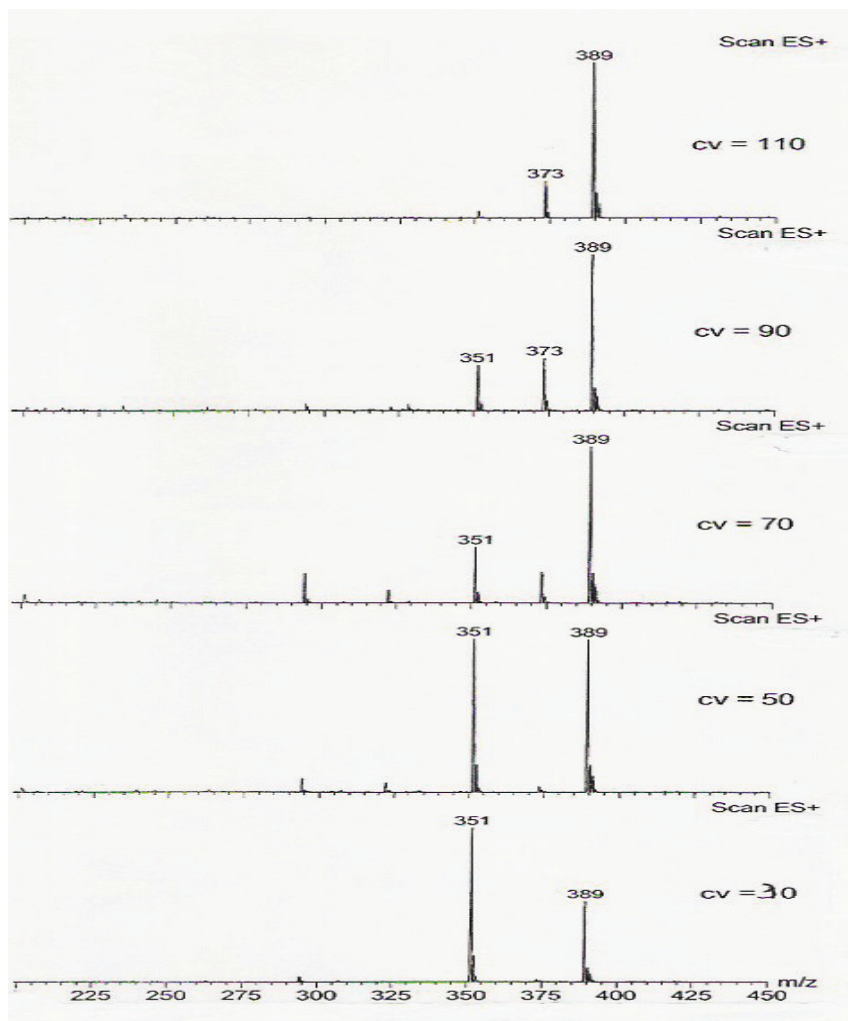
Figure 2. The ESI-MS spectra of 1:1 mixture of N-(2aminoethanoyl)aminom-ethyl-18-crown-6 with K+ depending on the cone voltage (cv). The protonated forms (351 (M+H)+) disappear with increasing cone voltage, when complexes (389 (M+K)+ with metal ions is stable and ratio of abundances signals [LK]+ / [LH]+ is increasing.

The general synthetic procedure consists in the substitution of aza- or crown ether to selected aminoacid with blocked functional groups

and further progressive unblocking of amine and carboxylic groups in N-pendant arms.

In order to construct N- (2-amino-4-carboxybutanoyl) derivatives of cyclic polyamines and azacrown ethers we carried out four-stage synthesis. Initially, Z-L-glutamic acid 5-tert-butyl ester (**a**) was used as substrate in reaction with pentafluorophenol (**b**) and N,N'-dicyclohexylcarbodiimide (**c**) in order to mask reactive and unbounded carboxylic group in reacting substance (**a**). After a removal of N,N'-dicyclohexylcarbamide, purified product (**a'**) of first step was used in the essential reaction of the synthesis discussed. It was reacted with one of the macrocyclic substrates in the presence of triethylamine (Et$_3$N) to provide one of the intermediate products respectively. Further conversion into stable final products (**1-4**) was then carried out in two-stage process and lead to unbounded amine and carboxylic group in N-pendant arms.

1,4,8,11 – tetra – N - (2-amino-4-carboxybutanoyl) - 1,4,8,11-tetraazacycloteradecane tetrahydrochloride (1) [5].

where R=
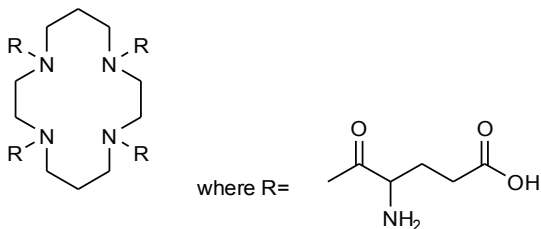
I. In a round bottom flask equipped with a reflux condenser, Z-L-glutamic acid 5-tert-butyl ester a (135 mg, 4 mmol), pentafluorophenol b (75.5 mg, 4.1 mmol) and N,N'-dicyclohexylcarbodiimide c (84.6 mg, 4.1 mmol) were dissolved in diethyl ether (100 ml). The reaction mixture was heated to boiling under reflux for 2h. Then it was allowed to cool to ambient temperature. The reaction was worked up by filtering off dicyclohexylcarbaimide and removal of the solvent. The resulting pale yellow oil (a') was used without further purification.

II. A solution of obtained oil **a'** (4 mmol) and 1,4,8,11-tetraazacyclotetradecane (cyclam) **1'** (20 mg, 1 mmol) with Et$_3$N (50.5 mg, 5 mmol) in diethyl ether (100 ml) was heated under reflux for 4d. The

etheric phase was washed with 0.1 M HCl and then with 0.1 M Na_2CO_3. The organic phase was dried ($MgSO_4$) and evaporated.

III. Icy acetic acid (2 ml) and palladium on active carbon (10%) (0.5 g) were added to a solution of N-substituted cyclam derivative **1''** (1 mmol) in dry methanol (100 ml), and then it was hydrogenated under atmospheric pressure and flushed with dry hydrogen until CO_2 was emitted (about 5h). The catalyst was filtered off and washed with hot methanol (20 ml). Combined methanol solutions were evaporated under vacuum.

IV. Obtained product (1 ml) was dissolved in trifluoracetic acid (TFA) (10 ml) and the solution was left for 24h. Then TFA was evaporated and the residue was dissolved in 2 M HCl (10 ml). The solvent was evaporated and the residue was purified by dissolution in dry methanol. Solvent removal gave flash-coloured crystals 1.

1,4,7,10,13,16 - hexa - N - (2-amino-4-carboxybutanoyl) - 1,4,7,10,13,16 - hexaazacyclooctadecane hexahydrochloride (2) [5].
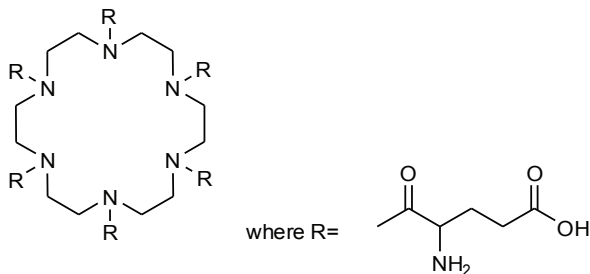
The compound **2** has been synthesized in agreement with the procedure for the compound **1**, except some distinctions that are specified below:

I. a (202.4 mg, 6 mmol), **b** (112.3 mg, 6.1 mmol), **c** (125.9 mg, 6.1 mmol);

II. a' (6 mmol), 1,4,7,10,13,16- hexaazacyclooctadecane (hexacyclen) **2'** (25.8 mg, 1 mmol), Et_3N (70.7 mg, 7 mmol) in acetonitryle.

1 – N - (2-amino-4-carboxybutanoyl) - 1 - aza - 15 - crown - 5 hydrochloride (3) [5].

where R=
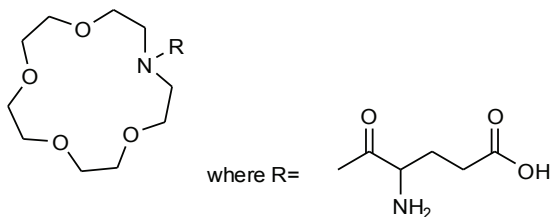
The compound **3** has been synthesized in agreement with the procedure for the compound **1**, except some distinctions that are specified below:

I. a (33.7 mg, 1 mmol), **b** (20.2 mg, 1.1 mmol), **c** (22.7 mg, 1.1 mmol);

II. a' (1 mmol), 1-aza-15-crown-5 **3'** (21.8 mg, 1 mmol) with Et_3N (12.1 mg, 1.2 mmol).

7,13 - di - N - (2-amino-4-carboxybutanoyl) - 1,4,10 - trioxa - 7,13 – diazacyclopentadecane dihydrochloride (4) [5].

where R=
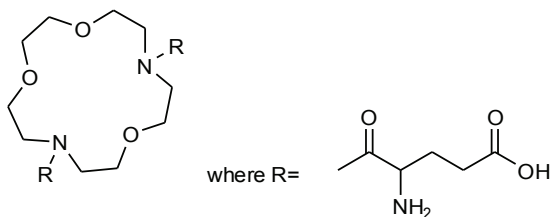
The compound **4** has been synthesized in agreement with the procedure for the compound **1**, except some distinctions that are specified below:

I. a (67.5 mg, 2 mmol), **b** (38.6 mg, 2.1 mmol), **c** (43.3 mg, 2.1 mmol);

II. a' (2 mmol),1,4,10-trioxa-7,13-diazacyclopentadecane **4'** (21.9 mg, 1 mmol) with Et_3N (50.5 mg, 2.5 mmol).

(1-(1-antraquinoyl)-7-(carboxymethyl)-1,7-diaza-12-crown-4 (5) [4].
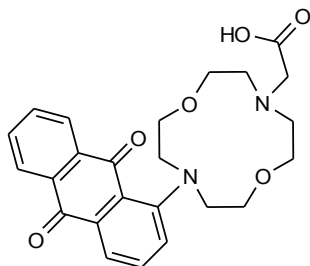
Compound **5** was obtained carried out three-stage synthesis. In the first stage 1,7-dioxa-4,10-diazacyclododecane (**a**) was used as substrate in reaction with 1-fluoroanthraquinone (**b**) previously prepared by standard diazonation reaction with $NaNO_2$ in acidic medium [6] in the presence of caesium carbonate (**c**).The aminoanthraquinone aza-crown ethers were reacted with t-butyl chloroacetate to form blocked with *t*-bytyl compound **5** in high yield. This compound without additional purification was used for the next step of the synthesis. The *t*-butyl group was removed by using CF_3COOH to yield **5**. The crude product was purified by ion-exchange chromatography (Sepharose Q, OH⁻ form) and then by flash chromatography on silica gel. Compound **5** was reacted with Boc-Lys-OH forming derivatives of aza- crown ethers and protected lysine in 72% yield [4]. This synthetic procedure allows to receive the entire series of different aza crown ether with different size of macrocyclic cavity .

I. A mixture of 1,7-dioxa-4,10-diaza-cyclodo-decane (**a**) (2 g, 11.5 mmol), 1-fluoroanthraquinone (**b**) (2.84 g, 12.6 mmol), caesium carbonate (**c**) (7.47 g, 23 mmol) and toluene (12 ml) was placed in a round-bottomed flask and maintained at 35 ºC for 48 h. After cooling to room temperature the reaction mixture was filtered and the precipitate rinsed with methylene chloride (60 ml). Next, the red organic layer was washed with 1M tetrabutylammonium hydroxide (50 ml), water (50 ml) and dried over anhydrous magnesium sulphate. The solid was purified using flash column chromatography on silica gel (eluting with CH_2Cl_2/ MeOH, 5/1) to afford 2.7 g of 2 as a red solid (62%).

II. A mixture of 1-(1,7-dioxa-4,10-diazacyclododecan-4-yl)anthracene-9,10-dione (1.5 g, 4 mmol), sodium carbonate (0.85 g, 8 mmol) and *t*-butyl chloroacetate (0.63 ml, 4.4 mmol) in acetonitrile (7 ml) was refluxed for 24 h. After cooling to room temperature, the mixture was filtered and the residue washed with methylene chloride (40 ml). The organic layer was washed with water (40 ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated to yield 1.86 g (94%) of the desired compound as a red solid; mp: 82 °C.

III. The trifluoroacetic acid (15 ml) was added to 1.2 g of compound obtained in the previously stage of synthesis (2.4 mmol) and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to dryness and the residue dissolved in water and purified using ion-exchange chromatography (Sepharose Q OH⁻ form, eluting with 0.01 M ammonium acetate). Water was evaporated and the residue was filtered though silica gel (eluting with AcOEt/MeOH, 1/1) affording 0.92 g of **5** as a red solid (86% yield); mp: 115 °C.

IV. Boc-Lys-OMe was added to a mixture of **5** (0.26 g, 0.6 mmol), N-Hydroxybenzotriazole (HOBt) (0.081 g, 0.6 mmol), Triethylamine (TEA) (0.246 ml, 1.8 mmol) in dichloromethane (4 ml), and the reaction mixture was stirred at room temperature for 4 h. Then 30 ml of dichloromethane was added, the organic layer was washed twice with water (40 ml) and dried over anhydrous magnesium sulphate. The solid was purified by flash column chromatography on aluminium oxide (eluting with CH2Cl2/MeOH 200:1) to afford 0.3 g of Boc-Lys-OH derivatives of (**5**).

N-(2aminoethanoyl)aminomethyl-18-crown-6 [6].
Gly-aminomethyl-18-crown-6
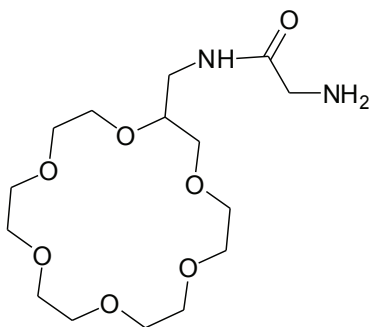
The compound **6** was obtained by the method with using of C pendant crown ether. To a clan dry round bottomed flask 1-hydroxybenzotriazole (HOBT) (**a**) 92.12 mg (0.68 mmol) and N,N'-dicyclohexylcarbodiimide (DCC) (**b**) 140.67 mg (0,68 mmol) were transferred along with mixture of 10ml of methylene chloride (DCM) and N,N-dimethylformamide (DMF). The mixture was stirred on an ice bath till all solids have dissolved. In separate vial Boc-GlyOH (**c**) 71.72 mg (0,68 mmol) was dissolved in 5 ml of DCM and added to the activated HOBT/DCC solution at 0° C. The reaction was stirred for 30 min. After this time 175mg (0,60 mmol) 1,4,7,10,13,16-hexaoxacyclooctadecane-2-methanamine (**d**) was added at 0° C. The reaction mixture was stirred overnight at room temperature and the white precipitate of N,N-dicyclohexylurea (DCU) was filtred off. After filtration, the obtained solution was evaporated to dryness. The residue was dissolved in 20 ml of methylene chloride and washed with water. The organic layer was dried on anhydrous $MgSO_4$ filtered and evaporated. The obtain crude product without further purification after dried was dissolved in 10 ml TFA/DCM (1:1) and stirred for 10h. The solution was concentrated in vacuo, and dissolved in methanol saturated HCl. The solution was evaporated to dryness and the residue was adsorbed on silica gel and purified by column chromatography with DCM/methanol. The crude product was crystallized from diethyl ether to afford compound **6** with total yield 89.0% (212 mg).

2,6-diamino-N-(aminomethyl-18-crown-6)hexanamide [7].
Lys- aminomethyl-18-crown-6
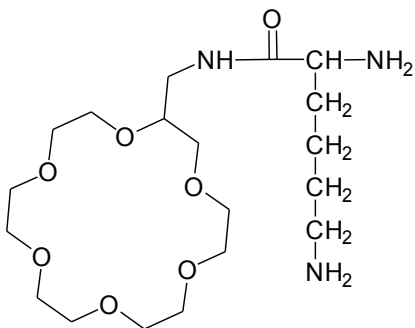
The compound **7** was obtained by the coupling reaction describd above with lysine. To the flask with 1-hydroxybenzotriazole (HOBT) (**a**) 108,3 12 mg (0,80 mmol) and N,N'-dicyclohexylcarbodiimide (DCC) (**b**) 165,10 mg (0,80 mmol) were transferred along with mixture of 10 ml of methylene chloride (DCM) and N,N-dimethylformamide (DMF). The mixture was stirred on an ice bath till all solids have dissolved.

In separate vial 375.00 mg (0,80 mmol) Fmoc-Lys(Boc)-OH (**c**) was dissolved in 5 ml of DCM and added to the activated HOBT/DCC solution at 0° C. The reaction was stirred for 30 min. After this time 240 mg (0,80mmol) 1,4,7,10,13,16-hexaoxacyclooctadecane-2-methanamine (**d**) was added at 0° C.

The reaction mixture was stirred 5h at room temperature, white precipitate of N,N-dicyclohexylurea (DCU) was filtred off. After filtration, the obtained solution was evaporated to dryness. The residue was dissolved in 20 ml of methylene chloride and washed with water. The organic layer was dried on anhydrous $MgSO_4$ filtered and evaporated. The obtain crude product without further purification after dried was dissolved in 15 ml of TFA/DCM (1:1) and stirred for 10h. The solution was concentrated in vacuo. The solution was evaporated to dryness. The crude product was treated with 20 ml 20% of piperidine in DMF to remove Fmoc group. The reaction was monitored on TLC using silica gel and purified by column chromatography with DCM/methanol. The crude

product was crystallized from diethyl ether to afford compound **7** with total yield 78.0% (268 mg).

**2-amino-5-guanidino-N-(aminomethyl-18-crown-6)pentanamide [8].
Arg- aminomethyl-18-crown-6**
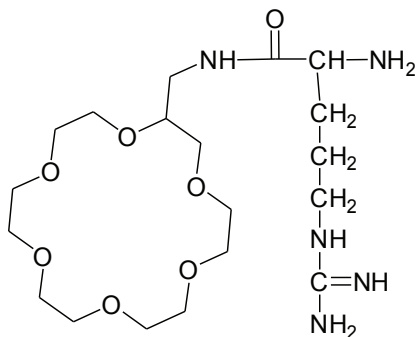
The compound **8** has been synthesized with total yield 91%, with the same procedure for the compound **7**, except some distinctions that are specified below:

a (114.83 mg, 0.85 mmol), **b** (175.37 mg, 0,85 mmol), **c** (551.45 mg, 0.85 mmol), **d** (250.00 mg, 0.85 mmol).

In the same synthetic procedure was obtained the same derivatives with aminomethyl-15-crown-5.

1-N-(2-amino-4-carboxybutanoyl)-1-aza-15-crown-5 hydrochloride [7].
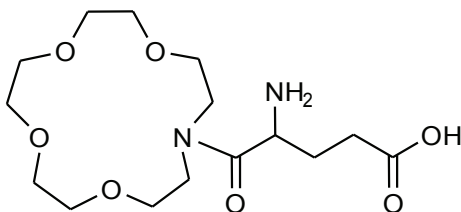
The compound **7** was obtained in multi-stage synthesis. In a round bottom flask equipped with a reflux condenser, Z-L-glutamic acid 5-tert-butyl ester, pentafluorophenol and N,N'-dicyclohexylcarbodiimide were dissolved in diethyl ether. The reaction mixture was heated to boiling under reflux for 2h. Then it was allowed to cool to ambient temperature. The reaction was worked up by filtering off dicyclohexylcarbaimide and removal of the solvent. The resulting pale yellow oil was used without further purification. A solution of obtained oil and 1-aza-15-crown-5 with Et_3N in diethyl ether (100 ml) was heated under reflux for 4d. The etheric phase was washed with 0.1 M HCl and then with 0.1 M Na_2CO_3. The organic phase was dried ($MgSO_4$) and evaporated. Icy acetic acid (2 ml) and palladium on active carbon were added to a solution of N-substituted derivative in dry methanol, and then it was hydrogenated under atmospheric pressure and flushed with dry hydrogen until CO_2 was emitted (about 5h). The catalyst was filtered off and washed with hot methanol. Combined methanol solutions were evaporated under vacuum. Obtained product was dissolved in trifluoracetic acid (TFA) and the solution was left for 24h. Then TFA was evaporated and the residue was dissolved in 2 M HCl. The solvent was evaporated and the residue was purified by dissolution in dry methanol.

The spectral data of product **7** flash-coloured oil; yield: 95.0 % (33 mg) (according to Z-L-glutamic acid 5-tert-butyl ester); ^{1}H NMR (DMSO, 300 MHz) 12.0 ppm, bs, 1H; 8.2 ppm, bs, 3H; 4.4 ppm, bt, 1H; 3.4-3.8 ppm, m, 20H; 2.4 ppm, m, 2 H; 1.9 ppm, m, 2H.

The general synthetic procedure in the substitution of C-pendant arm crown ethers to blocked lysine with anthraquinone as the functional group directly attached or separated with ethylene group, performing role of bridge between amino acid and anthraquinone.

In order to construct derivatives of crown ethers, anthraquinone and lysine we carried out two or three-stage of synthesis. The 1-fluoroanthraquinone (**a**) or mono O-tosylated anthraquinone (b) was used as substrate in reaction with protected lysine (c) and caesium carbonate (**d**). The coupling reaction of the modified amino acid (**c'**) formed in the previous stage and crown ethers (**e**) was realized using a standard coupling procedure in peptide synthesis (**f**) DCC- diisopropylcarbodiimid and HOBt-N-hydroxybenzotriazole. In the case of anthraquinone derivatives separated by ethylene bridge, this coupling method was inef-

fective, that is why we have decided on (**f'**) HOBt/TBTU method which gave satisfactory results.

Nα-Boc-L-Nε-(9,10-dioxo-9,10-dihydro-anthracen-1-yl)-lysine- amin-omethyl-18-crown-6 [8].
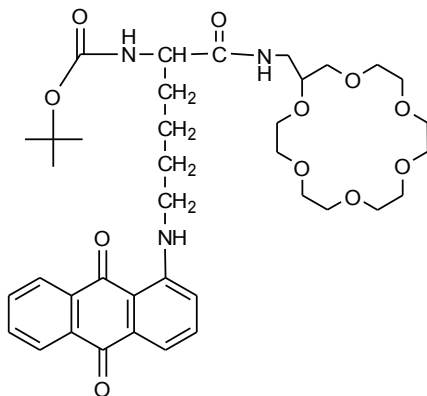
I. The mixture of (**a**) 1-fluoroanthraquinone (1.131 g, 5 mmol), (**c**) Boc-L-Lys-OH (1.231 g, 5 mmol) and (**d**) Cs_2CO_3 (3.528 g, 10 mmol) in toluene (10 ml) was placed in a reaction vial and kept at 80 °C for 24h (in an oil bath). After cooling to room temperature the reaction mixture was dissolved in CH_2Cl_2, filtered and partitioned between methylene chloride (50 ml) and 1 M HCl (50 ml). The organic layer was next washed with1M $KHSO_4$, water and brine and dried over anhydrous $MgSO_4$. The purple-red solid was purified using flash column chromatography (eluted with CH_2Cl_2/MeOH 4:1) affording 2.177 g of Boc-L-Lys(AQN)-OH as a red solid (90.8% yield). [7]

II. General procedure for preparation of N-substituted Nα-Boc-L-Nε-(9,10-dioxo-9,10-dihydro-anthracen-1-yl)-lysine by aminomethyl crown ethers.

The mixture of (**f**) HOBt 46,5 mg (0,33 mmol) and DCC 69,6 mg (0,33 mmol) in 10 ml CH_2Cl_2 was stirred on ice bath at 0°C till all solids have been dissolved. In separate vial (**c'**) Boc-Lys(AQ)-OH 138,9 mg (0,3 mmol) was dissolved in 5 ml of CH_2Cl_2 and then added to a mixture

of (**f**) HOBt/DCC. After 30 min to a reaction mixture was added (**e**) NH_2-CH_2-18-crown-6 90 mg (0,3 mmol) dissolved in 5 ml of CH_2Cl_2 and the reaction was left to stir at room temperature under argon for 24h. The reaction mixture was subsequently filtered, diluted with CH2Cl2 and washed with water. The organic fraction was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography eluted with CH_2Cl_2/MeOH 5:0.4 afford a pure products as a red solid (89.1% yield).

N$^{\alpha}$-Boc-L-N$^{\varepsilon}$-(9,10-dioxo-9,10-dihydro-anthracen-1-yl)-lysine-aminomethyl-15-crown-5 [9].
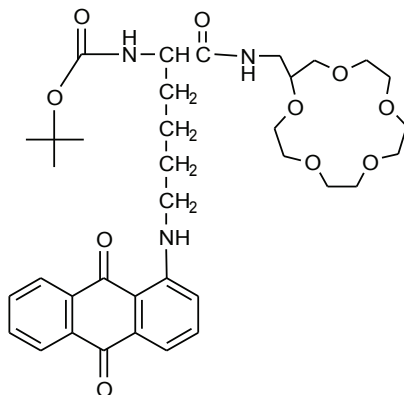
The compound **9** has been synthesized according to the general procedure for the compound **8**, except some distinctions that are specified below:

I. reaction in the same procedure;

II. f (1 mmol) HOBT, (1 mmol) DCC, **c'** Boc-Lys(AQ)-OH (1 mmol) **e** NH_2-CH_2-15C5 (1 mmol), yield of **9** 96.8%

Nᵅ-Boc-L-Nᵋ-(9,10-dioxo-9,10-dihydro-anthracen-1-yl)-lysine-4'aminobenzo-15-crown-5 [10].
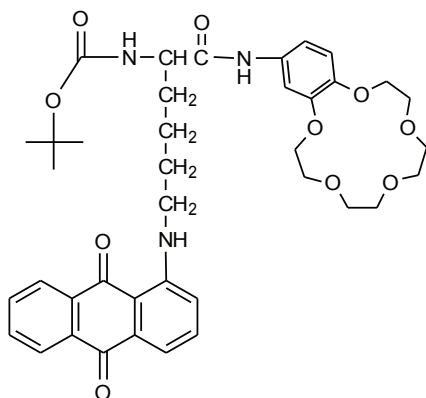
The compound **10** has been synthesized according to the general procedure for the compound **8**, except some distinctions that are specified below:

I. reaction in the same procedure;

II. f (0.7 mmol) HOBT, (0.7 mmol) DCC, **c'** Boc-Lys(AQ)-OH (0.7 mmol) **e** $NH_2-C_6H_3$-15C5 (0.7 mmol), yield of **10** 96.7%

Nᵅ-Boc-L-Nᵋ-(8-hydroxy-9,10-dioxo-9,10-dihydro-anthracen-1-yl)-lysine- aminomethyl-18-crown-6 (11).
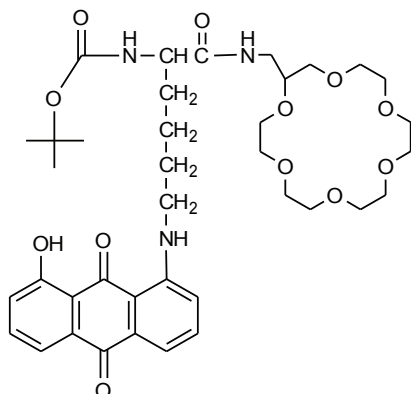
The general synthetic procedure in the substitution of C-pendant arm crown ethers to blocked lysine with hydroxy anthraquinone as the functional group.

I". The solution of 1,8-dihydroxyanthracene-9,10-dione (5,030 g, 20,9 mmol) and *p*-toluenesulphonyl chloride (5,350 g, 20,9 mmol) in 200 ml of CH_2Cl_2 in a round bottom flask was cooled to -10° C. The solution of 15 ml triethylamine in 100 ml of CH_2Cl_2 was added to the mixture reaction in a potion (10 ml) during 4h. The reaction mixture was stirred at room temperature 24h. The resulting solution was evaporated and the obtained yellow solid was dissolved in 200 ml of CH_2Cl_2, washed with water (3×150 ml), dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography eluted with CH_2Cl_2/petrol ether 4:1 afford a pure products as a red solid with 53.0% yield.

I'. The mixture of (**b**) 8-hydroxy-9,10-dioxo-9,10-dihydroanthracen-1-yl 4-methylbenzenesulfonate (1,610 g, 4 mmol), (**c**) Boc-L-Lys-OH (1,0 g, 4 mmol) and (**d**) Cs_2CO_3 (2,650 g, 8 mmol) in toluene (10 ml) was placed in a reaction vial and kept at 80° C for 24h (in an oil bath). After cooling to room temperature the reaction mixture was dissolved in CH_2Cl_2, filtered and partitioned between methylene chloride (50 ml) and 1 M HCl (50 ml). The organic layer was next washed with1M $KHSO_4$, water and brine and dried over anhydrous $MgSO_4$. The purple-red solid was purified using flash column chromatography (eluted with CH_2Cl_2/MeOH 4:0.5) affording 0,708 mg of Boc-L-Lys(1-OH-AQN)-OH as a red solid with 27.0% yield.

II. f (0.32 mmol) HOBT, (0.32 mmol) DCC, **c'** Boc-Lys(1-OH-AQ)-OH (0.32 mmol) **e** NH_2-CH_2-18C6 (0,32 mmol), yield of **11** 20,5%

The same procedure was used to the synthesis of monohydroxy derivatives anthraquinone and lysine in position 4, and 5, with aminomethyl-15-crown-5 and 4'-aminobenzo-15-crown-5**.**

The general synthetic procedure in the substitution of C-pendant arm crown ethers to blocked lysine with anthraquinone separated with ethylene group.

Nα-Boc-L-Nε-(9,10-dioxo-9,10-dihydro-anthracen-1-(ethylamino)-yl)-lysine- aminomethyl-18-crown-6 [12].
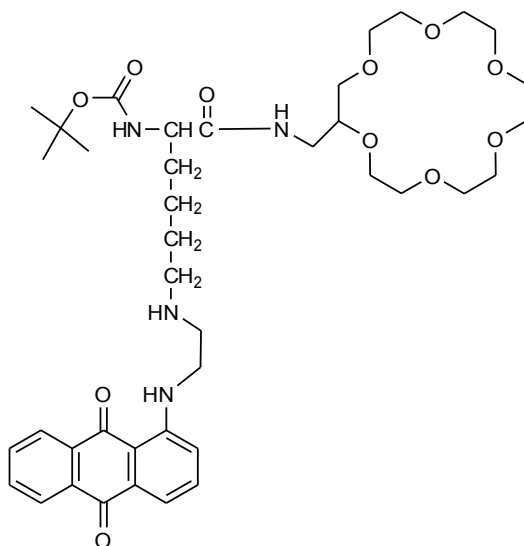
I". To the solution of 1-(2-hydroxyethylamino)anthracene-9,10-dione (3 g, 11.224 mmol) in 500 ml of CH_2Cl_2 was added triethylamine (0,155 ml ,11.224 mmol). Then the mixture was cooled to -10 °C and the *p*-toluenesulphonyl chloride (2.14 g, 11.224 mmol) was dissolved in CH_2Cl_2 and added in a portion to the reaction. The reaction was stirred at room temperature for 76 h. The resulting solution was evaporated under vacuum and again dissolved in 200 ml of CH_2Cl_2, next washed with ice water (5×150 ml) and dried with $MgSO_4$. After concentrated under vacuum. The residue was purified by flash column chromatography eluted with CH_2Cl_2 obtained a pure products as a red solid with 29.0% yield.

I'. The mixture of (**b**) 2-(9,10-dioxo-9,10-dihydroanthracen-1-ylamino)ethyl 4-methylbenzenesulfonate (300 mg, 0.656 mmol), (**c**) Boc-L-Lys-OH (162 mg g, 0.656 mmol) and (**d**) Cs_2CO_3 (428 mg, 0.656 mmol) in toluene (2 ml) was heated to 80ºC for 90h. After cooling to room temperature the reaction mixture was dissolved in CH_2Cl_2, filtered and partitioned between methylene chloride and 1 M HCl (50 ml). The organic layer was next washed with 1M $KHSO_4$, water and brine and dried over

anhydrous MgSO$_4$. The purple-red solid was purified using flash column chromatography (eluted with CH$_2$Cl$_2$/MeOH 5:1) affording 0,120 mg of Boc-L-Lys(Et-AQN)-OH as a red solid with 23.5% yield.

II. f' (0.1 mmol) HOBT, (0.11 mmol) TBTU, Et$_3$N (0,3 mmol) **c'** Boc-L-Lys(Et-AQN)-OH (0.1 mmol) **e** NH$_2$-CH$_2$-18C6 (0.1 mmol), yield of **12** 15.0%

N$^\alpha$-Boc-L-N$^\varepsilon$-(9,10-dioxo-9,10-dihydro-anthracen-1-(2-aminoethyl)(methyl)amino)-yl)-lysine- aminomethyl-18-crown-6 [13].
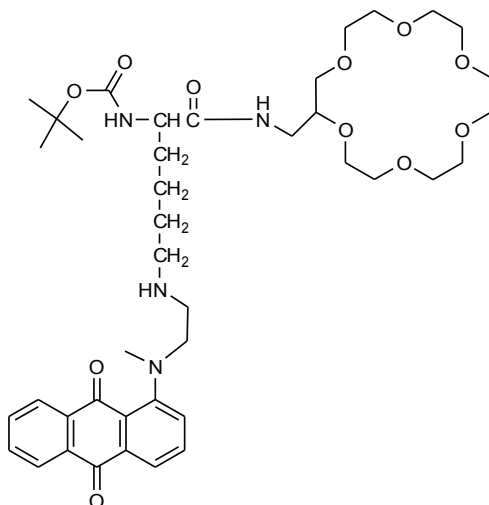

The compound **13** has been synthesized in agreement with the procedure for the compound **12**, except some distinctions that are specified below:

I". 1-((2-hydroxyethyl)(methyl)amino)anthracene-9,10-dione (1.0 g, 3.560 mmol), Et$_3$N (3.560 mmol), *p*-TsCl (0.68 g, 3.560 mmol), yield 15.0%;

I'. b (200.0 mg, 0.460 mmol), **c** (85.0 mg, 0.460 mmol), **d** (212.0 mg, 0.460 mmol), 49.4%;

II. f' (0.049 mmol) HOBT, (0.054 mmol) TBTU, Et$_3$N (0.147 mmol) **c'** Boc-L-Lys(Me-N-Et-AQ)-OH (0.049 mmol) **e** NH$_2$-CH$_2$-18C6 (0.049 mmol), yield of **13** 18.0%

N$^\alpha$-Boc-L-N$^\varepsilon$-(9,10-dioxo-9,10-dihydro-anthracen-1-(1-amino-2-methylpropan-2-ylamino)-yl)-lysine- aminomethyl-18-crown-6 [14].
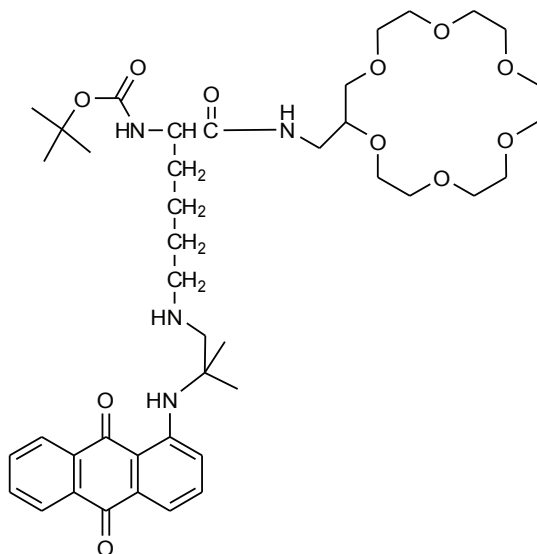
The compound **14** has been synthesized in agreement with the procedure for the compound **12**, except some distinctions that are specified below:

I". 1-(1-hydroxy-2-methylpropan-2-ylamino)anthracene-9,10-dione (3.0g, 10.158 mmol), Et$_3$N (10.158 mmol), *p*-TsCl (2.04, 10.158 mmol), yield 15.0%;

I'. b (200.0 mg, 0.445 mmol), **c** (81.0 mg, 0.445 mmol), **d** (203.0 mg, 0.445 mmol), 16.2%

II. f' (0.057 mmol) HOBT, (0.0627 mmol) TBTU, Et$_3$N (0,171mmol) **c'** Boc-L-Lys(N-Et(Me)$_2$-AQ)-OH (0.057 mmol) **e** NH$_2$-CH$_2$-18C6 (0.057 mmol), yield of **14** 21.0

Currently there is a noticeable developent of synthetic procedure method consisting the incorporation of 1,4,7,10-tetraazacyclododecane and its derivatives in the structure of peptides.

1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra-acetic acid tris(phenylmethyl) ester (15) [8].
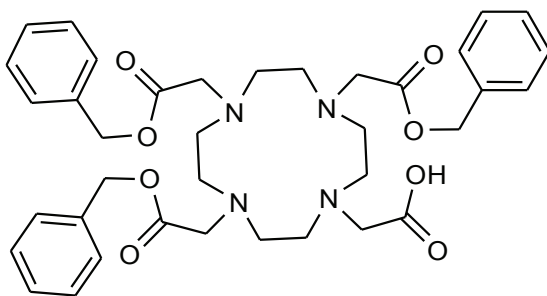
I. A solution of tert-butyl bromo-acetate (25.3 g, 130 mmol) in CHCl$_3$ (500 ml) was added dropwise in 7h to a solution of 1,4,7,10-tetraazacyclo-dodecane (112.3 g, 650 mmol) in CHCl$_3$ (2l) maintained under nitrogen at room temperature. After 14 h, the solution was concentrated to 800 ml, washed with H$_2$O (9 x 200 ml) to eliminate the excess of 1,4,7,10-tetraazacyclo-dodecane, dried over Na$_2$SO$_4$, and evaporated to give 1,4,7,10-tetraazacyclododecane-1-acetic acid 1,1-dimethylethyl ester (39 g, 99%) as a pale yellow oil.

II. A solution of 1,4,7,10-tetraazacyclododecane-1-acetic acid 1,1-dimethylethyl ester from previous synthesis (36 g, 126 mol) in DMF (200 ml) was added dropwise in 7h to stirred suspension of benzyl bromoacetate (94.96 g, 414 mol) and K$_2$CO$_3$ (86.8 g, 628 mmol) in DMF (250 ml) maintained under nitrogen at room temperature. After 4 h the suspension was filtered and the orange solution evaporated to dryness. The residue was dissolved in EtOAc (500 ml), washed with H$_2$O (3 x 400 ml) then with brine (2 x 300 ml). The organic phase was separated, dried over Na$_2$SO$_4$ and evaporated. The residue was purified by flash chromatography (CH$_2$Cl$_2$/MeOH 15:1) to give 5 (51 g, 51%) as a sticky pale orange solid of 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra-acetic acid 1,1-dimethylethyl tris(phenylmethyl)ester.

III. 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra-acetic acid 1,1-dimethylethyl tris(phenylmethyl)ester from previeous synthesis (47.11 g, 60 mmol) was dissolved in dioxane (500 ml), and then 12 N HCl (500 ml) was added under nitrogen at room temperature, obtaining

a white precipitate. After stirring for 16 h, the pale yellow suspension was evaporated and the residue dissolved in H_2O (700 ml) by ultrasound sonication. The solution (pH 2) was loaded onto an Amberlite XAD-16.00 resin column (900 ml) and eluted with a CH_3CN/H_2O gradient. The product elutes with 40% CH_3CN/H_2O. The fractions containing the product were concentrated to remove CH_3CN and then extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated. The pale yellow residue was triturated with EtOAc (150 ml) to give **15** (21 g, 52%) as a white solid.

4,7 ,10-Tricarboxymethyl-tert-butyl ester 1,4,7 ,10-tetraazacyclodo-decane-1-acetate (16) [9].
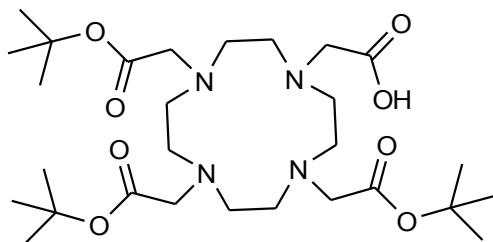
I. To a stirred solution of 1,4,7,10-tetraazacyclododecane (2.9 g, 16.8 mmol) in $CHCl_3$ (20 ml) was added benzyl bromoacetate (1340 ml, 8.4 mmol) in $CHCl_3$ (4 ml) within 1 h. Stirring was continued for an additional hour. The solution became cloudy (cyclen ·HBr). TLC control showed complete disappearance of the benzyl ester. The precipitate was filtered and the filtrate concentrated in vacuo. The resulting oil was purified by column chromatography $SiO2$ $CHCl_3/EtOH/NH_3$ 8:9:4 v/v). Evaporation afforded 1,4,7,10-tetraazacyclododecane-1-carboxymethyl-benzylester as an oil (2.3 g, 7 .2 mmol) in 85% yield.

II. To a stirred solution of product of synthesis **I** (1.41 g, 4.4 mmol) in acetonitrile (25 ml) was added K_2CO_3 (2.5 g, 18.1 mmol) followed by the dropwise addition of tert-butyl bromoacetate (2.65 ml, 18 mmol) in acetonitrile (5 ml) within 30 min. Stirring was continued for 2 h to complete the reaction. K_2CO_3 was filtered off and the solvent removed on a rotary evaporator. The resulting yellowish oil was immediately purified

by column chromatography (SiO$_2$ (35 g), cooling 8–10° C; gradient of CHCl$_3$ to CHCl$_3$/EtOH, 9:1, v/v). Evaporation of the solvent afforded an oil (2.9 g, 4.4 mmol) in 100% yield of 1,4,7,10-tetraazacyclododecane-4,7,10-tricarboxymethyl-tert-butylester-1-carboxymethyl benzylester .

III. Pd/C (10% Pd, 400 mg) was added to a solution of compound from **II** synthesis (2.92 g, 4.4 mmol) in THF/MeOH (1:1, v/v, 500 ml), and H$_2$ was bubbled through the solution at normal pressure. Hydrogenation was conducted for 5 – 12 h at normal pressure. The catalyst was removed by filtration through Celite. The solvent was evaporated to afford a pale yellow oil (2.5 g, 4.3 mmol) which was crystallised from acetone/diisopropyl ether by adding small amounts of HBr to afford the product **16** (2.9 g 3.3 mmol) in 74% yield.

1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid-tris-methyl ester (17) [10].
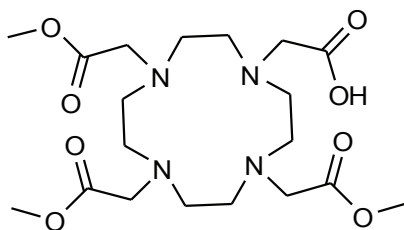
I. To a stirred mixture of 1,4,7,10-tetraazacyclododecane-1-carboxymethyl-benzyl ester, described abowe [9] (0.45 g, 1.4 mmol), and potassium carbonate 0.79 g, 5.7 mmol) in anhydrous acetonitrile (8 ml) was added methyl bromoacetate (0.54 ml, 5.7 mmol; dissolved in 2ml of CH$_3$CN) dropwise during 0.5 h. The reaction was allowed to proceed for additional 2 h before being filtered. The filtrate was concentrated in vacuo. Purification was performed on silica gel (eluent MeOH:CH$_2$Cl$_2$, 1:9, v/v). Yield of 1,4,7,10-Tetraazacyclododecane-4,7,10-tricarboxymethyl methyl ester 1-carboxymethyl-benzyl ester was about 0.45 g (60%).

II. Compound obtained above (0.35 g, 0.64 mmol) was dissolved in methanol (50 ml). Pd/C (10%, 55 mg) was added, and the mixture was hydrogenated at atmospheric pressure overnight. The mixture was filtered through Celite and concentrated. Then it was used for the next

step for the synthesis of oligonucleotides without further derivatization [10].

The studied compounds have ionic character. The selectivity of studied ionoreceptors determine size and type of crown ether, aminocrown ethers or cyclic amines as substitents in aminoacids. For all studied molecules it is observed two concurred processes: protonated and complexation.

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Chapter 6

Periodically organized mesoporous silica-based thin films – preparation and application

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1. Introduction

This article reviews synthesis, characterization (structures) and emerging current applications of ordered silica–based inorganic and inorganic–organic mesoporous films. Thin films of these groups of porous materials can be prepared by various techniques generally used for film formation from liquid solution, including solvent evaporation, in situ growth from solution, templating synthesis and other alternative methods. Although these methods allow control over the thickness and pore structures in thin films, they currently offer limited control over the pore alignment relative to the substrate surface. The ordered and properly aligned (perpendicularly or in parallel to the support) mesoporous thin films are highly promising for a range of potential applications in: separations, chemical sensing, molecular recognition, electronics and photonics. Furthermore, additional functionalization of the internal pore surfaces in such films and deposition of functional nanoparticles within the pores offer numerous new possibilities for molecular engineering.

2. Mesoporous thin films – historical background

According to IUPAC, ***mesoporous films*** refer to materials with pore diameters in the 2–50 nm ranges. The term "*film*" is used to describe an extremely thin continuous sheet of a substance in a specific planar

geometry that can be formed on any support (substrate) and that maybe or not in the intact with a substrate – Figure 1 [1]. The motivation for the preparation of the mesostructured inorganic and inorganic–organic mesoporous films has been receiving a great attraction over last fifteen years and originated especially from the appreciation of their technological potential as stated in the paragraphs 1 and 5 (especially as sensors, optical and electronic materials, and insulating layers of low dielectric constant for microelectronics) [2,3]. These applications require the ordered materials in the form of thin film that are characterized from one side by the bulk properties (such as symmetry, pore diameter and volume, surface area and stability) and from the other side by the film-related parameters (pore orientation, film thickness, continuity and surface roughness).
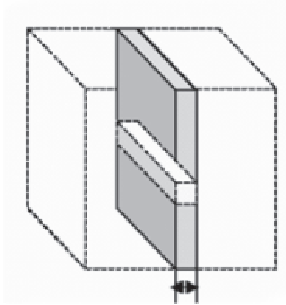
Figure 1. The schematic representation of the mesoporous film orientation. The bar represent the film dimensions: 2-50 nm.

The most commonly used technique for film synthesis is the sol–gel process [4] that, in the synthesis of mesoporous counterparts, comprises several approaches including casting, spin–coating, dip–coating, flow field induction, hydrothermal deposition and vapor infiltration, etc. The advantage of the sol–gel method lies in the fact that the mesoporous structure of the thin film as well as its macroscopic shape (morphology) can be controlled [5]. The first synthesis of mesoporous silica thin films was reported in 1994 and was done on glass by spin–coating using acidic surfactant–silicate gels [6]. It involved the mixing of tetramethyl orthosilicate (TMOS) and water followed by the addition of a surfactant,

i.e. alkyltrimethylammonium bromide (C_nTMABr) at a molar ratio of 1TMOS:0.15-0.50 C_nTMABr:$2H_2O$. The film was yielded by spin–coating of the above gel solution on the glass substrate, as the solvent evaporated. Unfortunately, the film had a lamellar structure after drying. Later on, free-standing mesoporous silica films with stable one– (1D) or two–dimensional (2D) pore structures were prepared from tetraethyl orthosilicate (TEOS) or TMOS under acidic conditions at air–water and oil–water interfaces [7-12]. Only decade of intensive research resulted in many reports on supported mesoporous silica films that were obtained from organic silicates under acidic conditions at liquid–solid interfaces on a variety of substrates such as glass, silicon, graphite, mica and oxides using casting, spin–coating and dip–coating methods [13–49]. However, one have to mention that during first years mostly disordered structures were reported. Only since 1997, the preparation of true family mesoporous silica films have been testified [18,19,21,41,42]. Supported MCM-41 and MCM-48 silica films were made under conventional basic conditions by hydrothermal deposition, which exhibited a good structural stability [50–53]. Very recently, a vapor–phase synthesis of mesoporous silica films has brought forth, i.e., mesoporous silica thin films with a hexagonal structure were synthesized under acidic or basic conditions, which showed a high structural stability [54]. Comparatively, casting seems to be convenient and efficient in the manufacture of silica ordered mesostructured thin films with controlled pore structure and morphology. However, the continued efforts are being made to amend the drawback of casting, i.e., serious structural shrinkage upon surfactant removal by calcination. The worse silicate polymerization can get reinforced by certain treatments following casting, e.g., vapor infiltration of silica source [54] and curing [55,56]. In order to suppress the structural shrinkage or distortion of thin films, low temperature surfactant removal methods, e.g., supercritical fluid extraction (SFE) [57], can be taken into consideration.

The mushrooming in the field of mesoporous silica films is illustrated in the Figure 2, which shows the evolution of the number of published scientific articles in this area of films obtained through surfactant templated growth since 1994/96. There are few review articles published in this area as well [e.g., 58–63].
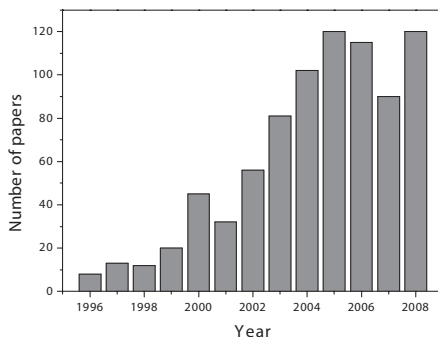
Figure 2. Published scientific articles in the field of mesoporous silica films (based on data from Scopus).

3. Preparation of films

While physical deposition methods are preferred when dense thin films are to be prepared, chemical deposition approaches are much more suitable for the preparation of thin porous layers (though the polycondensation of the inorganic precursors around organic supramolecular micellar assemblies at the substrate interface environs). In this approach, the mesoordering occurs through the evaporation induced self–assembly (EISA) mechanism. Other less known processes have been also used. Film growth by electrochemical techniques, at air–solution or substrate–solution interfaces (ASI or SSI respectively), by impregnation in vapor phase or in solution, polymer layer casting or even pulsed laser deposition (PLD) techniques, will be also discussed. However, these methods do not ensure good reproducibility and mesostructured control as well as EISA can do.

3.1 Solvent evaporation techniques

The solvent evaporation techniques involve formation of a liquid film containing: solvent, surfactant and silica precursor followed by the evaporation of the solvent. Several methods can be used to develop films. These include dip–, spin–coating and film casting. It is considered that solvent evaporation is a driving force for the organization of surfactant species into mesoscale aggregates (i.e., lamellar, hexagonal, cubic structures) around which condensation of silicate species takes
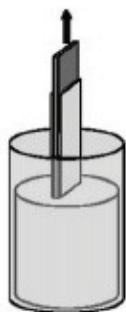
Figure 3. Scheme of dip–coating method procedure.

place. The various mesostructured inorganic films prepared by the solvent evaporation techniques are summarized in Tables 1–3 [64–96].

The mesostructured silica-based films prepared by a ***dip–coating*** method are shown in Table 1. In this method, the substrates are withdrawn from a homogeneous solution and the dip–coated matter is allowed to drain to a particular thickness – see Figure 3 [63]. The thickness of the film is mainly determined by the rate of evaporation of the solvent and the viscosity of the solution. One of the advantages of this method is the facile formation of films on non–planar surfaces.

Table 1. Ordered mesostructured silica-based films prepared by dip-coating.

Structure of silica	Precursors	Support	Reference
3D Cub	TEOS, EtOH, HCl, CTAB	Alumina	[42]
Hex and 3D Cub ‖	TEOS, EtOH, HCl, PEO-PPO-PEO	Silicon wafers and glass slides	[64]
2D Hex ‖	TEOS, PEO-PPO-PEO, EtOH, HCl, Pluronic F127	Si(100) wafers	[65]
Hex	TEOS, NPhAPTES, CTAB	Glass slide	[66]
Hex ‖	TEOS, CTAB, ethanol, H_2O, HCl	Glass slide	[67]
Hex	TMOS, NaOH, NH_3, H_2O, CTABr	Silicon wafers, borosilicate glass	[68]
1D Hex	TEOS, HCl, H_2O, F127, EtOH	Glass and silicon	[69]
1D Hex & Cub ‖	TEOS, HCl, H_2O, EtOH, Brij 56	SiO_2/Si and Au	[70]
3D Hex, c axes ⊥	TEOS, HCl, H_2O, CTABr, EtOH	Silicon wafers	[71]
Hex & Cub ‖	TEOS, HCl, H_2O, CTABr	Silicon	[72]
1D Hex, 3D Hex, lamellar	TEOS, CTAB, Brij 56, HCl, H_2O	Silicon	[73]
3D Hex & Cub ‖	TEOS, HCl, H_2O, gemini surfactants	Silicon wafers or glass	[21]
1D & 2D Hex ‖	TEOS, EtOH, HCl, H_2O, CTAB, F127	Glass or silicon wafers	[74]
Cubic & 3D Hex‖	TEOS, HCl, EtOH, CTAB	Silicon wafers	[19]
2D Hex	TEOS, CPTES, DEPPTES, P123	Glass	[75]

‖: Parallel to interface; ⊥: normal to interface.

Another method – spin–coating – has been widely used for the preparation of mesostructured films by solvent evaporation summarized in Table 2. Four stages of spin-coating can be distinguished: deposition of the surfactant/inorganic solution, spin-up, spin-off and evaporation [4]. Initially, an excess of liquid is deposited on the surface of the substrate during the first stage. In the spin-up stage, the liquid flows radially outward by centrifugal force – Figure 4. In the spin-off stage, the excess of liquid flows to the perimeter and leaves in a form of droplets. In the final stage, evaporation takes place leading to the formation of uniform thin films. One of the most important advantages of this method is that the film tends to become very uniform in thickness. The main disadvantage of this method is that it can only be used with flat substrates.
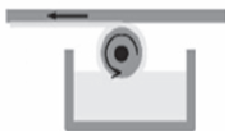
Casting (spreading/coating) is another solvent evaporation method that has been used for the preparation of mesostructured films. In this method, the solution is dropped on to the substrate and allowed to solidify, resulting in much thicker films. For example in spray–coating (Figure 5), the solution is pulverized onto the surface of the substrate using an aerosol generator or an atomizer.

Some examples of mesostructured films prepared by casting and modified casting techniques are shown in Table 3.

Table 2. Ordered mesostructured films prepared by spin–coating.

Structure of silica	Precursors	Support	Reference
Hex ‖	TMOS, HCl, C_nTAC	Pyrex glass	[76]
Hex ‖	TEOS, CTACl, HCl	Glass	[22]
3D Hex c-axis ⊥ to the film plane	TEOS, HCl, CTAB, ethanol	Glass plates	[33]
3D Hex⊥	TEOS, CTAB, HCl, ethanol	Glass plates	[77]
Hex ‖	TEOS, CTAC, HCl, Pluronic P123	Microslide glass, titanium, silicon	[78]
Disordered	TEOS, Pluronic P123, ethanol, poly(propylene oxide)	Si(100) single crystal or crystalline quartz	[79]
Oriented lamellar	silica TEOS, ethanol, HCl, Fe-TMA	Glass	[80]
Hex	Sodium silicate solution, H_2SO_4, CTACl	ITO-coated glass	[81]
Hex & Cub‖	TEOS, P123, F127, ethanol, H_2O, HCl	n-type silicon with SiO_2 and Si_3N_4	[82]
Hex	TMOS, NaOH, NH_3, H_2O, CTABr	Silicon wafers, borosilicate glass	[68]
1D Hex‖	TEOS, HCl, H_2O, P123	Glass	[77]
Hex ‖	TEOS, HCl, H_2O, P123	Glass	[78]
1D Hex & Cub‖	TEOS, HCl, H_2O, EtOH, Brij 56	Silicon with oxide layer (SiO_2/Si) and Au	[70]
Hex	TEOS, HCl, H_2O, CTAB, EtOH	Surface aluminum hydroxide on glass	[83]
1D Hex ‖	TEOS, HCl, H_2O, CTACl, PrOH	Glass	[84]
Lamellar, 1D Hex ‖	TEOS, HCl, H_2O, CTACl, PrOH	Glass	[85]
Hex & Cub‖	TEOS, HCl, H_2O, CTABr	Silicon	[72]
Lamellar, Hex & Cub	TMOS, CTACl, HCl, H_2O	Glass	[86]
Hex	BTESE, CTAB, EtOH, H_2O, and HCl	Glass	[87]
Hex	BTESB, H_2O, EtOH, HCl, CTAB	Silicon substrates	[88]
mesoporous	TFPTMOS +TMOS	Silicon substrates	[89]

‖: Parallel to interface; ⊥: normal to interface.

Table 3. Ordered mesostructured films prepared by casting.

Structure of silica	Precursors	Support	Reference
Hex ‖	TEOS, CTAC, HCl	Functionalized Si(100) wafers	[90]
Hex‖	TEOS, $C_{12}EO_{10}$, $C_{16}EO_{10}$, $C_{16}TAC$, HCl, H_2O	Silica glass substrate coated with polyimide film	[91]
Hex‖	TEOS, CPC, H_2O, HCl	Glass slides	[11]
Hex‖	TEOS, HCl, H_2O, gemini surfactants, alkyl ammonium bromides (C_{12}–C_{18})	Glass	[12]
Hex‖	TEOS, HCl, H_2O, CTACl	Silicon wafers	[92]
Hex‖	TEOS, HCl, H_2O, CTACl	Mica–gold layer	[93]
Hex‖	TEOS, HCl, H_2O, CTABr, EtOH	Unsupported	[94]
Lamellar, 1D Hex & Cub	TEOS, PrOH, HCl, CTACl, H_2O	Glass	[28]
2D Hex	TMOS, NaOH, NH_3, CTAB, CTAHS	Silicon or glass	[95]

‖: Parallel to interface.

Very attention-grabbing approach for one step synthesis of highly ordered nanoporous organosilica thin films with rather large pores (about 6 nm of diameter), bi-functionalized by two distinct organic groups, was also reported by Mehdi et al. [75]. The highly ordered hybrid mesoporous multifunctional thin films were obtained by co-condensation of TEOS and a mixture of two different organotriethoxysilanes groups (3-cyanopropyltriethoxysilane and 3-diethylphosphonatopropyltriethoxy silane) in a variable ratio and in the presence of Pluronic P123 surfactant as template under acidic conditions (Figure 6).
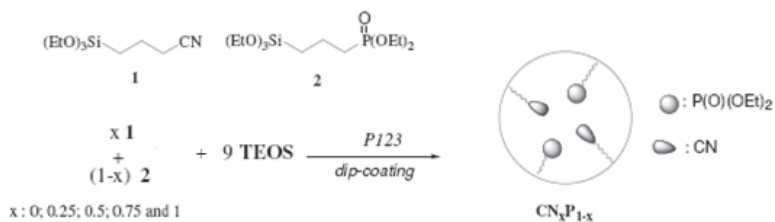
Figure 6. Scheme for the highly ordered hybrid mesoporous multifunctional thin films formation.

In a very interesting alternative synthesis approach, Chan et al. [96] prepared three-dimensional cubic ceramic mesostructured films via spin–casting by employing silicon containing triblock copolymers. In this proposed method, a bifunctional oxidation process consisted of ozonolysis and UV radiation, was used to selectively remove hydrocarbon blocks and convert the remaining silicon-containing template composite into a mesostructured silicon oxycarbide.

To conclude, different pore structures (i.e., hexagonal, cubic, lamellar) and pore symmetries (P6mm two–dimensional hexagonal, Ia3d cubic, P63/mmc three–dimensional hexagonally packed spherical micelle, etc.) with one–, two– and three–dimensional pores have been observed on the films prepared by these three methods (Figure 7).
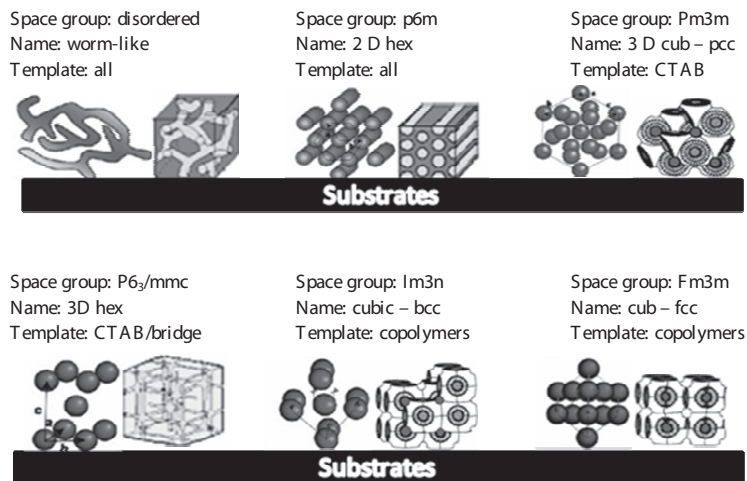
Figure 7. Possible pore structures and symmetries observed on the mesoporous films.

However, the control over pore orientation relative to the substrate surface still remains a major synthesis challenge for two–dimensional hexagonal structures in particular, because the pore alignment normal to the substrate surface is required for making these pores accessible in membranes and thin films (Figure 8).
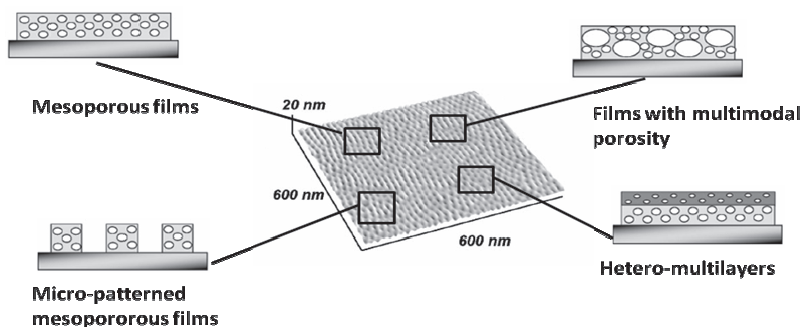
Figure 8. Complex architectures for mesoporous films.

3.2 Growth from solution

The principle for the synthesis of ordered mesoporous films by growth from solution is to bring the synthesis solution (consisting of solvent, surfactant and inorganic precursor) in contact with a second phase, e.g., solid (ceramic, mica, glass), gas (air, helium) or another liquid (oil). The two–phase system is kept under specific conditions and thus the ordered film is formed at the interface. When the second phase is solid, it is the support on which the ordered film is grown, whereas when the second phase is air or oil then the solid films are self–standing. The formation of the ordered films in the presence of different second phases is briefly discussed below.
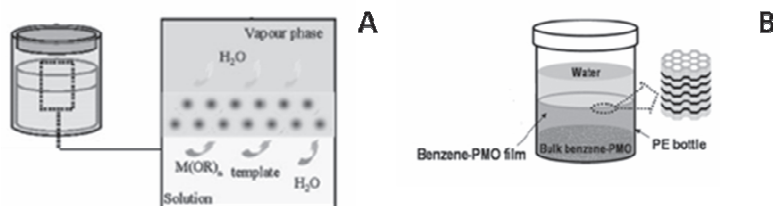
Figure 9. Scheme of interface growth (A) and illustration for free-standing benzene-organosilica film with crystal-like wall structure (B).

Ordering of inorganic–surfactant species can occur spontaneously at the **solid support interface** submerged in the synthesis solution. It has been shown that films of this type grow only in acidic solutions [97].

The first example of silicate–surfactant films formed spontaneously from an acidic synthesis medium on mica substrates was reported by Yang et al. [15]. Some of the relevant work on growth of mesostructured films at the solution–support interface [98–101] is summarized in Table 4. Mostly three–dimensional cubic and two–dimensional hexagonal films with pores oriented parallel to the substrate have been reported. Interestingly, Tolbert et al. [18] reported two–dimensional hexagonal films that nucleate on micellar structures in an oriented fashion and then grow into the solution.

Table 4. Ordered mesostructured films grown at solution–support interface.

Growth method	Pore orientation	References
Heteronucleation of 2D Hex phase	disordered	[16,98]
Nucleation in applied dc field	slightly distorted 2D Hex ‖ along flow path	[99]
Micromolding, colloidal sphere templating	3D Cub, 2D Hex ‖	[100]
Si "Rubbing method" for polyimide overlayer	2D Hex ‖	[22,101]

‖: parallel to interface

Yang et al. [8] reported for the first time an example of a free–standing silicate–surfactant film spontaneously grown at the **air–solution interface** (ASI). The films were prepared from dilute acidic solutions. The silicate film formation was proposed to occur by the polymerization of silicate species in the surfactant head group regions of the hexagonal phase that was concentrated at the liquid surface overstructure [102]. Three–dimensional hexagonal silicate films have been grown at the air–water interface [18]. Mesostructured films grown at the air–solution interface are summarized in Table 5.

Growth at an oil–solution interface involves the solubilization of the silica precursor in the oil phase. When separated from the aqueous solution, the silica precursors react with the surfactant at the oil droplet interface forming the desirable mesoporous silica particles (i.e., hexagonal or cubic). The most representative examples of films grown at the oil–solution interface are shown in Table 6.

Table 5. Ordered mesostructured films grown at air–water interface.

Precursors	Pore orientation	References
Dilute acidic TEOS and $C_{16}TACl$	2D Hex ∥	[8,103–105]
Dilute acidic TEOS and $C_{16}TAB$	2D Hex ∥	[10,106]
Dilute acidic TEOS and $C_{16}TAB$	3D Cub, 2D Hex∥	[107]
Dilute acidic TMOS and $C_{16}TAB$	2D Hex ∥	[25,38]
Alkaline TEOS and $C_{16}TAB$	Disordered 2D Hex	[108]
Dilute acidic TEOS and gemini surfactants	3D Hex with pore component ⊥	[18]
Dilute acidic TEOS and $C_{16}TACl$	Hex & Cub ∥	[98]
Dilute acidic TEOS and PEO–PPO–PEO triblock copolymers	2D Hex and 3Cub ∥	[109]
Acidic TEOS, glycerol–H_2O and $C_{16}TAB$	disordered mesostructure	[110]

∥: parallel to interface; ⊥: normal to interface.

Table 6. Ordered mesostructured films grown at oil–water interface.

Growth method	Pore orientation	Reference
TEOS in oil (n-C_6H_{14}, C_6H_6, toluene, mesitylene) HCl in water, $C_{16}TAB$ at interface	2D Hex ⊥ to interface	[9]
TEOS in oil (n-C_7H_{16}), HCl in water, and $C_{16}TACl$ at interface	2D Hex ∥ to interface bicontinuos Cub	[111]
TEOS in oil (n-C_7H_{16}), NaOH in water, and $C_{16}TAB$ at interface		

∥: parallel to interface; ⊥: normal to interface.

There are many alternative methods that combines the above mentioned techniques, for example impregnation of copolymer layers that consists in preparing a first layer of pure template, (e.g., block copolymers) and placing this layer into a saturated vapor phase of the inorganic precursor (e.g., deposited onto a substrate by spin-coating) in the presence of the appropriate catalyst (e.g., ammonia or HCl vapor) [112,113]. The volatile inorganic precursor is first adsorbed on the template layer and diffuses into the layer to eventually undergo hydrolysis/condensation. Polycondensation thus takes place around the templates that have to be eliminated to liberate porosity.

3.3 Alternative deposition techniques

Alternative deposition techniques reported to date include electrodeposition and pulsed laser deposition. Few mesostructured inorganic or inorganic/organic films prepared by these techniques are summarized in Table 7. Electrodeposition was recently proposed by Shacham et al. [116]. The basic idea is to manipulate the 'two-step' sol-gel preparation procedure [4] by an electrochemical control of the pH at the electrode/solution interface [117]. Starting from a sol solution where hydrolysis is optimal (i.e., pH 3) and condensation very slow, it is possible to accelerate polycondensation rates by applying a negative potential likely to increase pH at the electrode/solution interface and to generate a silica film on the conductive surface. Such local pH-driven sol–gel film formation resembles the electrolytic deposition of metal hydroxides upon reducing water to increase pH locally, thus hydrolyzing the metal ions in the vicinity of the electrode surface [118,119]. The film thickness is affected by the applied potential, the electrodeposition time, and the nature of the electrode. Moreover, it was clearly demonstrated that film deposition really occurred via an electrogenerated–base mechanism and not via electrophoretic deposition, which was otherwise applied to deposit sol–gel films but under high electric fields [120,121].

Another related approach is the electrochemical tuning of the solubility of trimethoxysilyl-group-modified monomers to derivatize electrode surfaces with organosilica networks [122]. After the pioneering work on the electrodeposition of methyltrimethoxysilane on indium-tin-oxide and gold electrodes, the method was extended to the tetramethoxy orthosilicate (silane) precursor to form nonfunctionalized silica films on various conducting substrates upon the electrochemical generation of OH^- species arising from water and/or oxygen reduction [123]. On the other hand, electrochemically driven pH decrease was also applied to prepare silica films from colloidal solutions under strictly aqueous conditions [124].

Electrodeposition can be achieved by combining the formation of a self–assembled "nanoglue" on the electrode surface, the sol–gel process, and the electrochemical manipulation of pH to catalyze polycondensation of the precursors. Gold electrodes pretreated with mercaptopropyltrimethoxysilane (MPTMS) were immersed in sol solutions containing the selected precursors (tetraethoxy orthosilicate,

Table 7. Ordered mesostructured films prepared by alternative deposition techniques.

Film type	Precursors	Support type	Deposition method	Reference
Hexagonal silica ⊥ to substrates	SiO_2, NaOH, CTAB, H_2SO_4	Si or SS porous substrates	Pulsed laser deposition	[24]
silica	TEOS, MPTMS, C1PTMS, PhTMS, CTAB, HCl	Gold, platinum, and glassy carbon electrodes	Electrodeposition	[114]
	TEOS, APTS, MPTMS	Gold electrodes pretreated with mercaptopropyltrimethoxysilane (MPTMS)	Electrodeposition	[115]

SS: Stainless steel; ⊥: normal to interface.

TEOS, in mixture with (3-aminopropyl)triethoxysilane, APTES, or MPTMS) where they underwent a cathodic electrolysis to generate the hydroxyl ions that are necessary to catalyze the formation of the organosilica films on the electrode surface [115]. Proton consumption near the electrode's surface catalyzes the sol–gel polycondensation of an organosilane such as methyltrimethoxysilane (MTMS, Equation 1) and thus ensures the electrodeposition of a thin layer of organosilica (Equation 2) at the surface of the substrate:

$$MeSi(OMe)_3 + 3H_2O \rightarrow MeSi(OH)_3 + 3MeOH \qquad (1)$$
$$MeSi(OH)_3 \rightarrow Me_nSiO_pH_q + H_2O \qquad (2, \text{unbalanced})$$
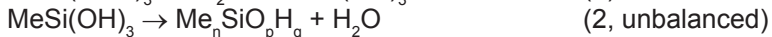
Pulsed laser deposition (PLD) is another alternative deposition technique for creating continuous mesoporous thin films on non-planar surfaces. The laser ablation process involves irradiating a bulk mesoporous target with an intense laser beam, which results in the ejection and deposition of nanoscale fragments of the mesoporous structure on a substrate surface. Balkus Jr. et al. [24] have developed a guest–assisted laser ablation technique, which consisted of exchanging the bis(pentamethylcyclopentadienyl)cobaltocenium ion ($Cp_2^*Co^+$) or ferrocene followed by PLD. The exchanged species absorbed the UV laser irradiation during ablation preventing the generation of defects in the bulk mesoporous structure and resulting in deposition of ordered

mesoporous films. Although the pulsed laser deposition method can produce good quality ordered mesoporous films, sophisticated equipment is required for the film manufacture. It is unlikely that this method will be able to compete with solvent evaporation techniques in speed and degree of control over resulting film structures and pore orientations.

4. Synthesis mechanism

Whatever the selected method of preparation, three main steps are involved in the preparation of mesoporous films. The first step consists of selecting *the chemical (inorganic silica) precursor, the catalyst, the templating agents, and the solvents*. The second step is the deposition process that drives both templating and silica inorganic precursors to combine in order to obtain a homogeneous layer with specific final mesostructure. Thus, the first stage of the reaction is to eliminate the templating agent to liberate the porosity and the second – to solidify the network.

As already reported in paragraph 3.1, chemical solution deposition methods, involving evaporation induced self–assembly, are the most often used to synthesize ordered mesoporous thin films. From a chemical point of view, the synthesis of silica films could be done in an acidic or basic medium, but the majority of thin films involve acidic catalysis. It is well-known that the molecular-scale morphology of silica differs when grown above (branched polymeric structures) or below (more particulate cluster morphology) the isoelectric point (pH=2).

The main templating agents that have been used to process films are amphiphilic ionic or nonionic molecules or polymers. Among them are CTAB, Brij, and commercially available block copolymers: F127, P123 (PEO–PPO–PEO).

Almost all silica mesoporous films are prepared from TEOS, whereas mesoporous organosilica films are synthesized using alkoxysilane with a bridging organic group (($R'O)_3Si–R–Si(OR')_3$) ($R'= –CH_3$ or $–C_2H_5$, R = ethane, ethylene, thiophene, and benzene) [125,126] or a cyclic siliquioxane precursor ($[C_2H_5O]_2SiCH_2]_3$) (examples in Figure 10) [127].

Porosity, pores, and inorganic wall sizes are governed by the size of the micelles and the surfactant/Si molar ratio in the solution. In general, triblock copolymers lead to thicker pore walls, bearing microporosity,

than smaller ionic surfactant. Thin films made with triblock copolymers (F127) are less stable than those prepared with ionic surfactants (CTAB) as a result of the microporosity created by the penetration of the PEO chain into the silica atomic network [128]. Typically, ionic surfactant micelles are strongly dependent on the ionic strength of the solution and on the size of the directly interacting ions.
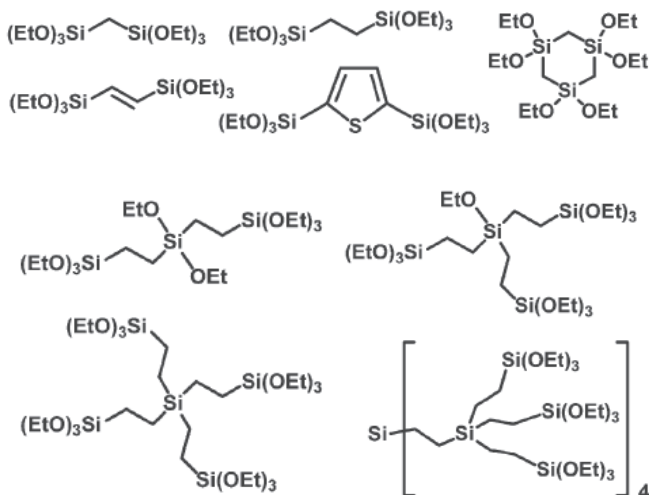
Figure 10. Potential silica precursors.

As-prepared thin films are hybrid xerogels where the organic template domains are embedded into the inorganic matrix, which are wet and poorly condensed. Making them useful as porous matrixes involves the stabilization of the inorganic network and the removal of the organic phase. Several treatments can be combined (e.g., thermal, chemical, extraction, UV, microwave, etc.). The more universal is the thermal treatment that allows simultaneously the dehydration, the decomposition of the surfactant, the condensation, and for some systems, crystallization [34].

For the polymer based organic/inorganic hybrid composites, polyimides have been applied. Poly(4,4'–oxydianiline biphenyltetracarboxamic

acid) (BPDA–ODA PAA) was used as the polyimide precursor, while the organosilica was made using o–substituted, m–substituted, and p–substituted phenyl organosilica precursor isomers. Finally, these precursor films were converted to corresponding polyimide/organosilica hybrid films by the thermal imidization of BPDA–ODA PAA, which results in poly(4,4'–oxydianiline biphenyltetracarboximide) (BPDA–ODA PI) [129].

5. Possible applications

Mesoporous silica–based films with their unique properties, e.g., versatile framework nature (single or multioxides, crystalline or amorphous structure, hybrid organic–inorganic, etc.), high surface area, modulable and controlable pore dimension and shape (cylindrical, spherical, ellipsoidal, etc.), tailored surface (organic or inorganic, inert or active), and high processing and handling abilities have offered to scientists a land of opportunities. Thus the mesoporous silica–based films can be used as:

➢ **electrochemical sensors** to detect simple molecules in gas phase as water [44, 130-132] alcohol [44,133,134], ammonia [130], NO [135,136] NO_2 [136, 137] and H_2 [138] or metal ions (Pb^{2+}) in aqueous phase [139]. Generally, pure silica films are deposited by dip–coating on substrates with metallic interdigitated electrodes.

➢ **capacitance–based sensors** (with pure or hybrid silica–based films) [130,135,140] to serve as insulator between a metallic conductor and a semiconductor. Variations of the films dielectric constant, which result from physical and/or chemical adsorption of the target gas inside the pores leads to changes of the capacitance. Such devices allowed good detection of water [130], ammonia [130], NO [135,136] and NO_2 [135] gases. The response could be modulated by the functionalization of films. For example, HDMS-treated films displayed a better dynamic range of the response toward relative humidity than pure silica films [130]. Yantasee et al. [139] tested the applicability of a thiol-functionalized film as an electrode sensing layer in the aqueous phase in the process of absorptive stripping voltammetry detection of Pb(II).

➢ **optical sensors** that operates by recording the emission of the

anchored fluorescein dye, for example pH sensitive. The dye conjugation is usually achieved during the synthesis of mesoporous films by covalent anchoring (i.e., by reacting fluorescein isothiocyanate with 3-aminopropyltriethoxysilane [141], by adding aminopropyltrimethoxysilane to a TEOS/Brij56 sol [142,143]) or after the synthesis (functionalization with triethoxysilyldibenzoymethane (SDBM) [144]). Optical sensors based on hybrid films containing organic bridges were also reported for the detection of Cu^{2+} in the aqueous phase [145,146], the determination of pH [147], and the detection of methanol vapor [148]. Surprisingly, for these sensors working in aqueous media, the leaching of the dyes was hardly observed.

➢ **quartz crystal microbalance** consisting of a quartz disk with double sides coated with metal electrodes modified with sensitive receptor molecules (β-cyclodextrin [149,150] to be used as sensors in (bio) chemical analysis.

➢ **insulators in integrated circuits with low-k dielectric properties**. Dielectric materials with a low dielectric constant k are currently in demand, because devices are becoming smaller. Two strategies to lower the dielectric constant are targeted: (i) increase the porosity and (ii) decrease the molecular polarizability of the matrix. Additional lowering of the k value can be accomplished by replacing the Si–O bond with a less polarizable bonds such as Si–R, thus by introducing alkyl or fluoroalkyl groups in the matrix. Therefore the different approaches involve the modification of either the nature of the walls (i.e., bridges polysilsesquioxanes [113,125,126] or methyltriethoxysilane [113,151,152]) or the pore surfaces with one-pot synthesis functionalization with perfluoralkoxysilanes [153] or trimethylchlorosilanes [154].

➢ **photonic materials** due to the fact that the regions provided by the core of micelles are compatible environments for organic dopants such as dyes, enhancing their overall solubilities, preventing their aggregation, protecting and stabilizing the embedded species. The intrinsic optical and mechanical properties of such new materials allowed scientists to elaborate materials exhibiting amplified spontaneous emission [105,155–158], to make a dye–doped mesostructured silica distributed feedback laser [155,159] and optical

data storage device [160].

➢ **environmentally responsive systems** to provide 'active' functionality such as dynamically controlled, by external stimuli (e.g., pH [161] temperature [162,163] or light [162,163]), features such as wetting properties, reduced dielectric constants, or enhanced adsorption of metal ions. One of the beautiful example of environmentally responsive mesostructured hybrid films is polymer/silica nanocomposite [161] with lamellar mesophases, which swell/deswell upon change of pH or temperature due to the presence of anchored polymers into the interlamellar space. Also trans ↔ cis isomerization of azobenzene derivatives can be used due to their UV sensitibility. This isomerization changes the molecular dimension of the organic molecule as shown in Figure11 [162,163].
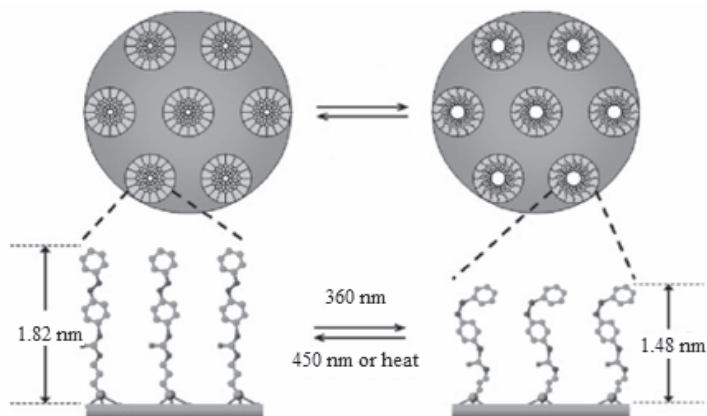
Figure 11. Photoresponsive nanofilm – scheme of operation.

➢ **permselective membranes** that prevent two phases from getting into the contact. They must be permselective to allow only some components of one phase to diffuse into the other, which explains why their transport properties depend on their microstructure, especially their pore size distribution and their connectivity [164].

➢ **gas permeation systems** consisting of the top dual layer ameliorating significantly the membrane quality (no pinhole defects resulting in higher selectivity between CH_4, H_2, He, and CO_2 gases) and attaining

higher gas permeation fluxes (thinner filtration layer allowed) if compared to the simple top layer [165].

> **ultrafiltration membrane**, for example as pH responsive ultrafiltration (UF) of polymer solutions membrane [166]. Upon filtration property, the combined effect of the silica nature of the membrane, whose surface charge can be easily adjusted by changing the pH, and the nonconnected cylindrical shape of the pores provides a new pH-responsive retention property, as proved by the filtration of poly(ethylene oxide) polymers (PEO) with different molecular weights.

6. Conclusions and Outlook

This review presents study on the major innovations in the field of periodically organized mesoporous films obtained via surfactant templated growth of pure inorganic or hybrid (organo)silica. Future developments of such films will probably occur in many fields, for example in the area of magnetic based devices and memories, (bio)chemical sensors, new mesoporous hosts having polymeric nanovalves (that can be thermally or chemically, e.g., pH-controlled) designations [e.g., 167]. Biocarriers for the controlled release of drugs, new materials for implants, multifunctional carriers associating hyperthermia treatments, controlled release of active components, and targeting and imaging, of tumors, represent just few novel aspects for biomedical applications [e.g., 168]. Mesoporous films can be also used as exotemplates to produce nanotubes (metallic nanowires, CNT, etc.), as hosts for conducting organic polymers, nanoparticules, clusters, organic dyes, and organometallic. Also the use of chiral surfactants can induce the formation of "chiral" porous networks with particularly original architectures. It is worthy to stress that the final aim of all these methodologies will be to tailor complex hierarchical structures possessing multiple functionalities in registry, enabling reactions to external 'stimuli' and even developing a certain degree of 'intelligence' [e.g., 163].

To conclude, the synthesis of new useful porous films possessing hierarchical structures opens up lands of opportunity in numerous areas. However even today, one major challenge that remains open, is the ability to selectively and accurately localize proper functionalities across the different length scales.

Acknowledgement

Glossary:

2D	two–dimensional
3D	three–dimensional
AIS	substrate–solution interfaces
APTES	(3-aminopropyl)triethoxysilane,
Brij XX	poly(ethylene oxide) alkyl ether surfactant; $R(EO)_xOH$, e.g., Brij 30 – $CH_3(CH_2)_{11}(EO)_4OH$; Brij 56 – $CH_3(CH_2)_{15}(EO)_{10}OH$; Brij 76 – $CH_3(CH_2)_{17}(EO)_{10}OH$;
BTESA	1,2-bis(triethoxysilyl)ethane
BTESE	1,2-bis(triethoxysilyl)ethene
BTESB	1,4-bis(triethoxysilyl)benzene
C_nTMACl	alkyl(C_n)trimethylammonium chloride
C1PTMS	chloropropyltrimethoxysilane
CPC	cetylpyridinium chloride
CPTES	3-cyanopropyltriethoxysilane
CTAB	cetyltrimethylammonium bromide
CTAC	cetyltrimethylammonium chloride
CTAHS	cetyltrimethyl ammonium hydrogen sulfate
Cub	cubic
DEPPTES	3-diethylphosphonatopropyltriethoxysilane
EO	ethylene oxide
EtOH	ethanol
EISA	evaporation induced self–assembly
F127	$HO(EO)_{106}(PO)_{70}(EO)_{106}H$
Hex	Hexagonal
HMS	Hexagonally-ordered Mesoporous Silicas
MCM	Mobil Composition of Matter
MCM-41	Hexagonally-ordered Mesoporous Silicas from MCM family
MCM-48	MCM family representative with cubic structure
MPTMS	3-mercaptopropyltrimethoxysilane
MTES	methyltriethoxysilane
MTMS	methyltrimethoxysilane
ODTMAB	Octadecyltrimethylammonium bromide
NPhAPTES	3-(2,4-dinitrophenylamino)propyltriethoxysilane
P123	$HO(EO)_{20}(PO)_{70}(EO)_{20}H$
PhTMS	phenyltrimethoxysilane
PLD	Pulsed Laser Deposition
PEO	poly(ethylene oxide) block
PPO	poly(propylene oxide) block
PrOH	propyl alcohol
PXXX	triblock copolymer – poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide – $HO(EO)_x(PO)_y(EO)_xH$
SBA-15	Santa Barbara Amorphous mesoporous material
SFE	supercritical fluid extraction
SSI	substrate–solution interfaces
TEOS	tetraethoxy orthosilicate
TFPTMOS	3,3,3-trifluoropropyltrimethoxy orthosilicate (silane)
TMOS	tetramethoxy orthosilicate

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